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UNIVERSITY OF ALBERTA

SYNTHETIC APPLICATIONS OF THIOLESTERS AND STUDIES ON THE TOTAL SYNTHESIS OF α-PATCHOULENE

BY

© WEIDE LUO

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Fall, 1991

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ISBN 0-315-69959-0

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DEGREE: DOCTOR OF PHILOSOPHY

YEAR OF THIS DEGREE GRANTED: 1991

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled SYNTHETIC APPLICATIONS OF THIOLESTERS AND STUDIES ON THE TOTAL SYNTHESIS OF α-PATCHOULENE submitted by WEIDE LUO in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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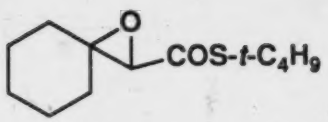
ABSTRACT

The first part of this thesis describes several new synthetic aspects of the thiolester functionality. It has been shown that the reduction of thiolesters could be effected in aprotic solvents using tetrabutylammonium borohydride as a reducing agent, producing primary alcohols as the major products. Glycidic thiolesters (*e.g.* **55**), readily prepared from α-bromothiolesters and carbonyl compounds by Darzens glycidic ester condensation, were shown to undergo reduction with Raney nickel to give 1,3-diols. With sodium borohydride at room temperature and lithium aluminum hydride at -78°C, the reduction of glycidic thiolesters was shown to proceed regioselectively to give 2,3-epoxy alcohols. A practical method for the preparation of α-bromothiolesters has been developed based on the trapping, with a thiol, of the α-bromoacyl bromide produced by Hell-Volhard-Zelinsky reaction.

An extensive study on the total synthesis of α-patchoulene (**74**) has been carried out. Results are described in the second part of this thesis. By a six-step reaction sequence including the skeletal rearrangement of **109**→**95**, 10-camphorsulfonic acid was efficiently transformed to bicyclic diketo alcohol **95**. For the construction of C ring, three synthetic approaches based on intramolecular aldol condensation reaction and McMurry diketone coupling reaction were examined and advance intermediates **123**, **127**, **136**, and **152** were prepared from diketo alcohol **95**.



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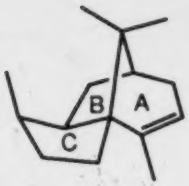

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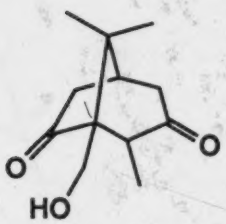

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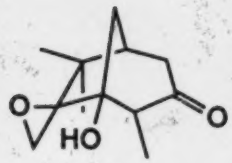

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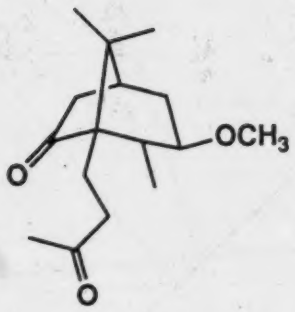

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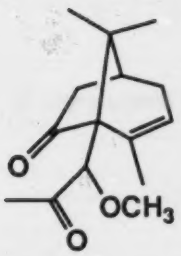

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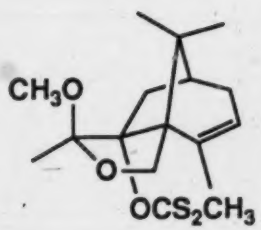

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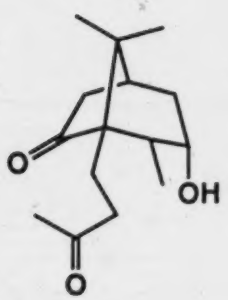

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ACKNOWLEDGEMENT

The author would like to express his utmost gratitude to his research director, Professor H. J. Liu, for his outstanding guidance, comments, and encouragement throughout this work. His particular interest and assistance during the preparation of this thesis are greatly appreciated.

The author is greatly indebted to Dr. T. T. Nakashima, Dr. A. M. Hogg, and Mr. R. N. Swindlehurst and their associates for recording the nmr spectra and all the mass spectra. Thanks are also due to the technical staff members in the microanalytical laboratory for the elemental analyses. He also wishes to thank Dr. M. Ralitsch for his enlightening discussion on chemistry and assistance in the preparation of this thesis, and Dr. L. K. Ho for his collaboration in the early stage of the work.

Finally, the author would like to thank the University of Alberta for financial support in the form of a Teaching Assistantship.

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
APT	Attached proton test
Ar	Aryl
Bu	Butyl
bs	broad singlet
CI	Chemical ionization
CoA	Coenzyme A
d	doublet
DCC	1,3-Dicyclohexylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide
eq	equivalent(s)
ir	infrared
LDA	Lithium diisopropylamide
m	multiplet
mol eq	molar equivalent(s)
MCPBA	*meta*-Chloroperoxybenzoic acid
ms	Mass spectrum
nmr	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDCP	Phenyl dichlorophosphate
Ph	Phenyl

Py	Pyridine
q	quartet
s	singlet
t	triplet
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPP	5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine

CHAPTER I

SYNTHETIC APPLICATIONS OF THIOLESTERS

INTRODUCTION

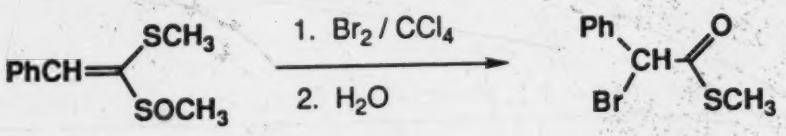
Although the first preparation of a thiolester, *S*-ethyl thioacetate, was reported as early as 1875,[1] the major development of thiolester chemistry was not made until the 1960's, when the importance of the condensation of acetyl-CoA in biological systems had been recognized[2] and the application of thiolester chemistry became widespread in organic synthesis.[3]

Up to this date, many successful methods have been developed for the preparation of thiolesters.[4] In practice, carboxylic acids[5] or their derivatives, such as halides,[6] anhydrides[7] and esters,[8, 9] have been most commonly used as starting materials, while mercaptans, metal thiolates,[10, 11] thioethers,[12, 13] phenyl isothiocyanate[14] and methylene sulfite[15] have been utilized as the precursors of the thiol moiety in thiolesters in various procedures. For carboxylic acids and esters, activating reagents such as 1,3-dicyclohexylcarbodiimide (DCC),[16, 17] phenyl dichlorophosphate,[18] or diphenylphosphoryl chloride[19, 20] are required to activate the C-O bond by forming intermediate complexes in the reactions.

α-Halothiolesters, as a group of thiolesters, could be synthesized using some of the general methods for the preparation of simple thiolesters.[21, 22, 23] For example, *S*-ethyl α-bromothioacetate was successfully prepared from α-bromoacetyl bromide and ethyl mercaptan in the presence of triethylamine. The same thiolester was also synthesized

from α-bromoacetic acid using DCC as an activating reagent. However, special methods for the formation of this group of thiolesters have also been recorded in the literature.

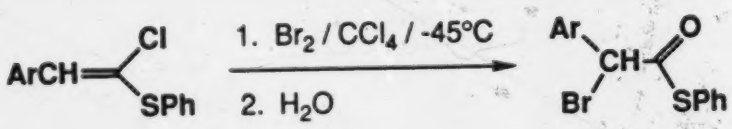
In 1975, it was reported by Ogura *et al.* [24] that bromination of 1-methylsulfinyl-1-(methylthio)-2-phenylethylene (**1**) in carbon tetrachloride followed by hydrolysis afforded *S*-methyl α-bromophenylthioacetate (**2**) in 25% yield (Scheme 1).



1 **2**

Scheme 1

Employing 1-chloro-1-alkenyl phenyl sulfides **3**, a similar method was developed by Fortes and Chaves.[25] They found that treatment of these compounds with bromine followed by hydrolysis gave *S*-phenyl α-bromothiolesters **4** in yields of 35-55% (Scheme 2).

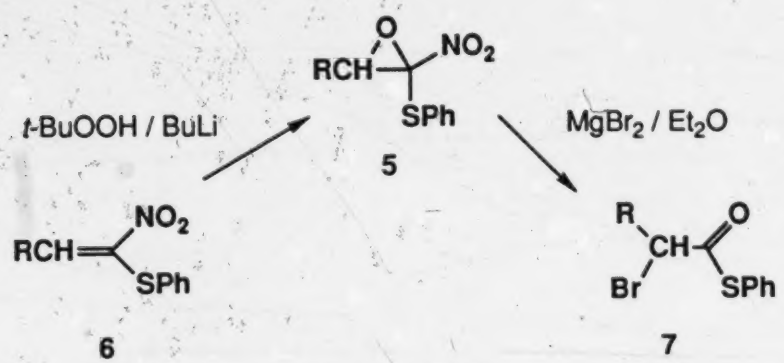


3 **4**

Scheme 2

Recently, Ashwell and Jackson[26] showed that 1-nitro-1-phenylthiooxiranes **5**, readily prepared by epoxidation of the

corresponding 1-nitro-1-alkenyl phenyl sulfides **6**, reacted efficiently under mild conditions with metal halides to give α-halo-substituted *S*-phenyl thiolesters **7** (Scheme 3).

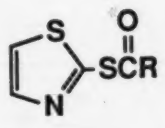


Scheme 3

In the study of the chemical behaviour and synthetic applications of thiolesters, the reduction of thiolesters with Raney nickel was among the earliest areas of interest. It was found that under the action of Raney nickel, a thiolester could be reduced either directly to a primary alcohol[27] or selectively to the aldehyde stage,[28, 29] depending on the reactivity of the catalyst used.

The reduction of thiolesters with lithium aluminium hydride was reported to give mainly alcohols and thiols,[30, 31, 32] and the reduction with lithium hydride (prepared from lithium and hydrogen) resulted in the formation of aldehydes.[33] The Clemmensen reduction was investigated by Mayer and coworkers.[34] They showed that the reduction of thiolesters to sulfides was possible only in the aromatic series.

The reduction of thiolesters with sodium borohydride to alcohols was first observed by Fujita[35] on highly active thiolesters such as compound **8**. Later, It was reported by Liu and coworkers[36] that ordinary thiolesters were also affected, and that a thiolester group could be selectively reduced in the presence of other carboxy-derived funtional groups such as amide, ester and nitrile. However, a large excess of the reducing agent was required for completion of the reaction due to the consumption of the reagent in protic solvent such as ethanol over a long period of reaction time.



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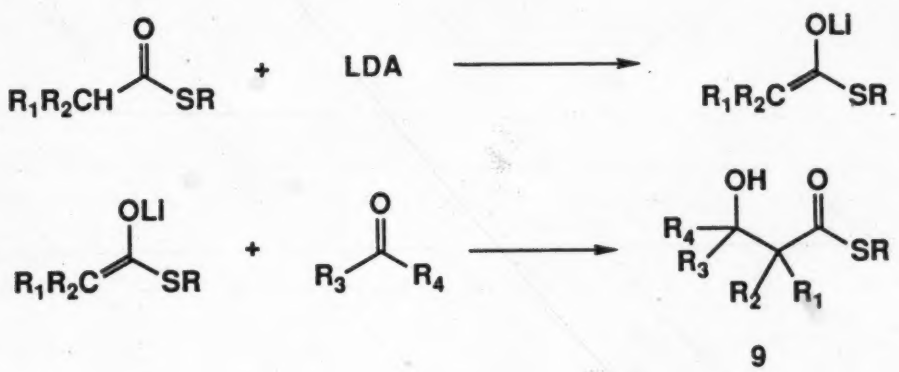
Another interesting area of study was on the formation of thiolester enolate ions, their nucleophilic addition to carbonyl compounds and subsequent transformation of the products. In 1929, the Claisen ester condensation of *S*-ethyl thioacetate was observed by Baker and Reid.[37] In 1975, Wemple[38] reported that enolates were formed from thiolesters upon treatment with lithium diisopropylamide at -78°C, and that β-hydroxythiolesters **9** were readily formed when ketones were added (Scheme 4). He and coworkers also successfully carried out the Darzens synthesis of glycidic thiolesters **10** and demonstrated their rearrangement reaction induced by boron trifluoride in diethyl ether (Scheme 5).[39, 40] In their investigation, 2-bromo- and 2-chlorothiolesters

were subjected to reactions with several carbonyl compounds, including acetone, cyclohexanone, benzaldehyde and isobutyraldehyde. The formation of glycidic thiolesters was effected under the action of non-nucleophilic bases such as sodium hydride and lithium bis(trimethylsilyl)amide. It was found that 2-bromothiolesters gave higher yields of products than the corresponding chloro compounds.



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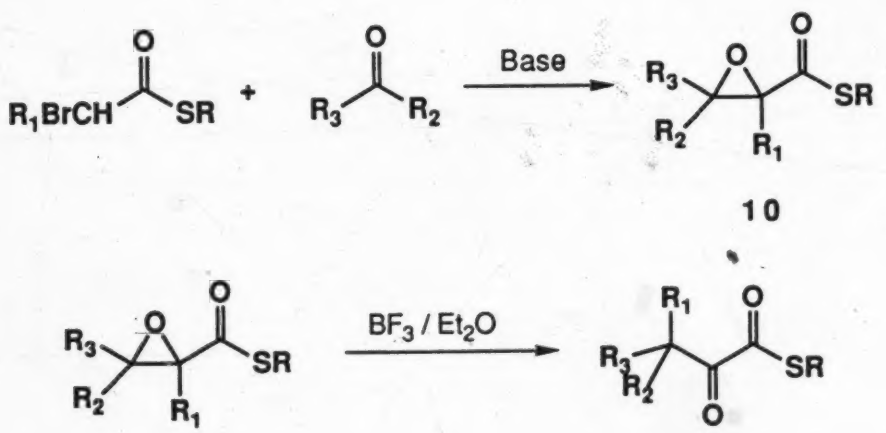
Scheme 4



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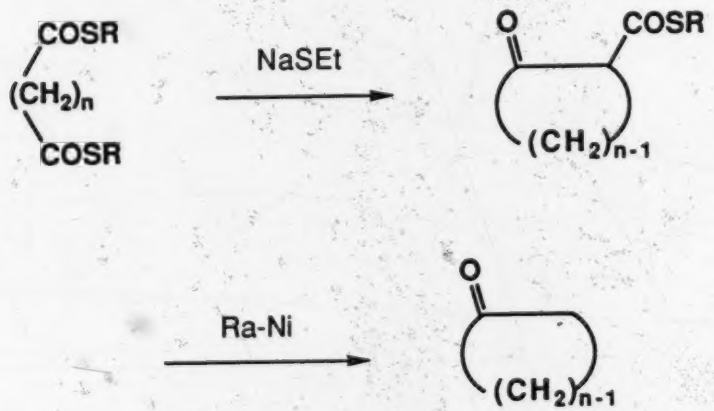
Scheme 5

It was reported by Liu and Lai in 1979 that the Dieckmann cyclization of ω-dithiolesters was easily effected by treatment with sodium hydride and a catalytic amount of ethyl mercaptan at room temperature.[41] The removal of the thiolester group from the resulting β-keto thiolesters was accomplished readily using Raney nickel[42] (Scheme 6). Liu and coworkers also demonstrated the feasibility of using *S*,*S*'-diethyl dithiomalonate (**11**) as an ethanol carbanion equivalent in alkylation[43] (Scheme 7) and Michael reactions[44] (Scheme 8).

In 1978, Gerlach[45] successfully used the Michael addition reaction of a silyl enol ether **12**, derived from a thiolester, to cyclopentenone as the key step in their synthesis of (±)-jasmineketolatone (**13**) (Scheme 9). In the next year, an intramolecular Wittig reaction of a thiolester, leading to fused azetidione-pyrroline antibiotics **14**, was described by Ponsford and coworkers[46, 47] (Scheme 10).



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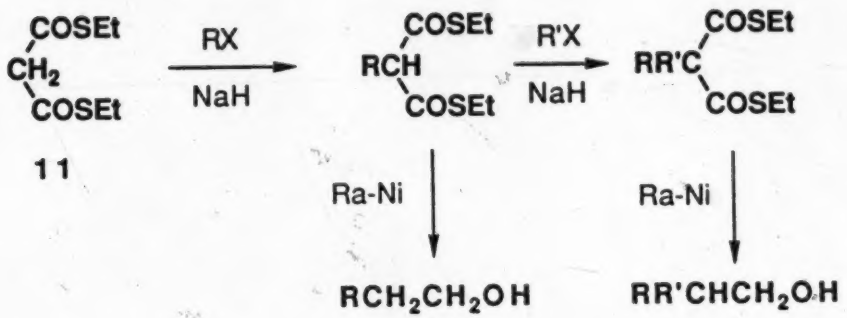
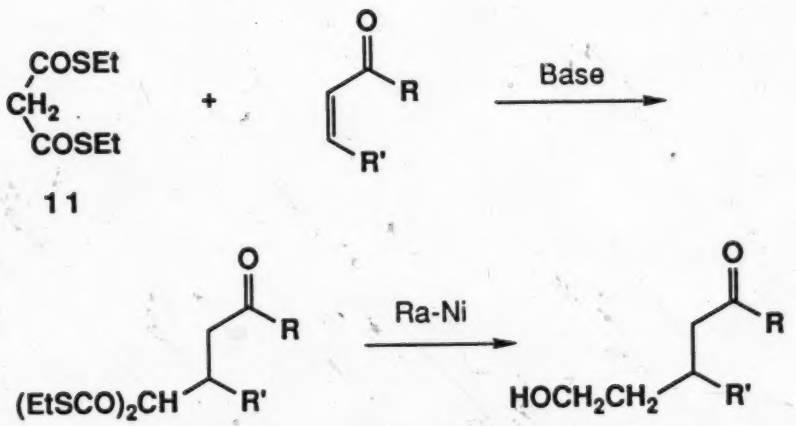


Scheme 7

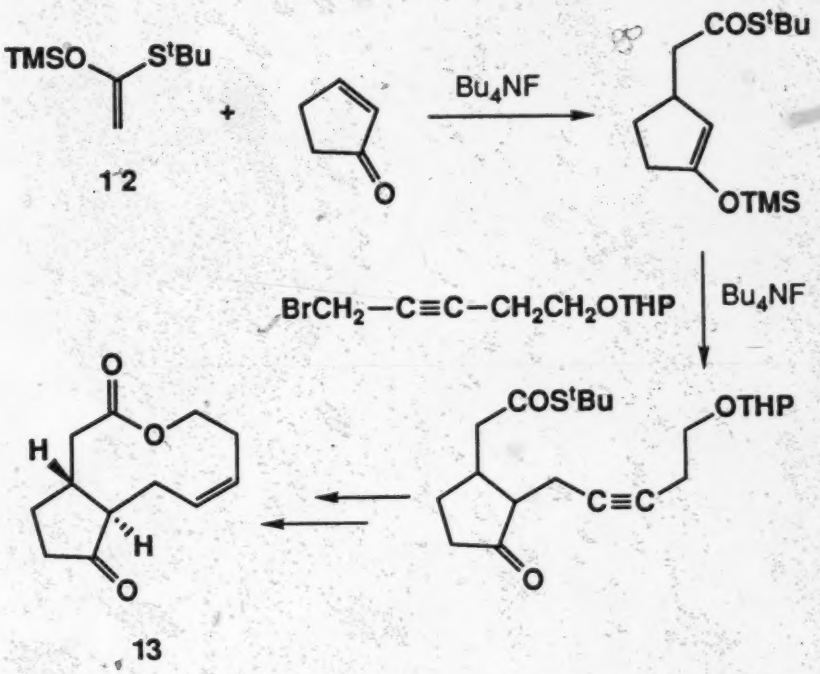


Scheme 8

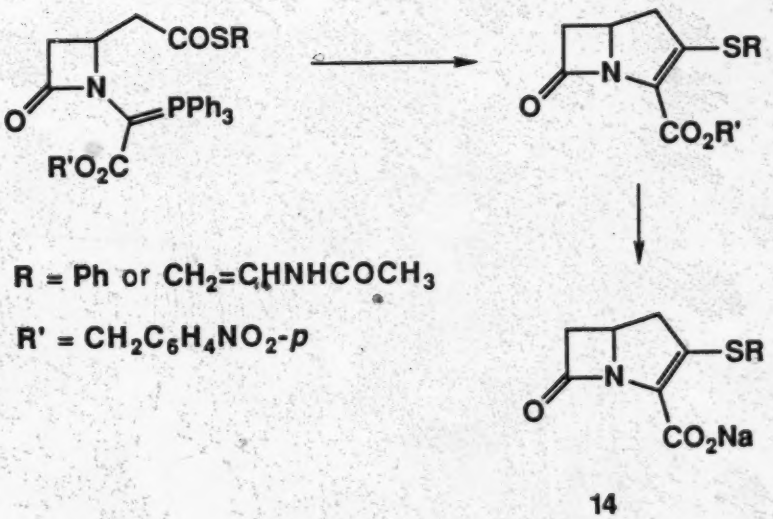
In the last three decades, these and many other investigations have uncovered a large number of interesting features of the thiolester functionality in organic synthesis. However, in comparison with its oxygen analogue, the understanding of the chemistry of this functionality and the discovery of its synthetic applicability are still quite limited. For a long time, thiolester chemistry has been one of the major areas of research in this laboratory. In the study on the reduction of thiolesters

with sodium borohydride,[36, 48, 49] it has been demonstrated that the thiolester group is highly useful as a latent hydroxymethyl unit in synthesis, especially, when such a unit, with or without protection, can not be directly involved in a desired transformation.

In continuation of our studies on the synthetic applications of thiolesters, the potential use of tetrabutylammonium borohydride as a mild reducing agent in aprotic solvent has been examined. We have also explored the reduction of glycidic thiolesters with a number of reducing agents including Raney nickel, sodium borohydride, and lithium aluminum hydride. During the course of these studies, a convenient practical method for the preparation of α-bromothiolesters has been developed and some interesting features of glycidic thiolesters have been uncovered. These results are discussed in Chapter I of this thesis.



Scheme 9



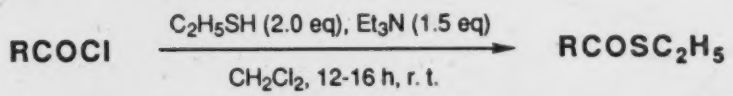
Scheme 10

RESULTS AND DISCUSSION

1. Reduction of thiolesters with tetrabutylammonium borohydride

For this study, a number of thiolesters were synthesized. Compounds **15-20** were obtained from the reactions of the corresponding acid chlorides with ethanethiol in the presence of triethylamine. In a typical experiment, ethanethiol (2 equivalents) was added dropwise to a solution of 2-naphthoyl chloride and triethylamine (1.5 equivalents) in methylene chloride at 0°C. Then the reaction mixture was stirred at room temperature overnight. Addition of aqueous sodium bicarbonate solution followed by extraction with methylene chloride and flash chromatography of the crude product on silica gel, eluting with ether-hexane (1:20), gave thiolester **19** in 93 % yield. Compounds **21-24** were prepared directly from the appropriate carboxylic acids according to the procedure described by Liu and Sabesan,[18] using phenyl dichlorophosphate as an activating reagent. The yields for the thiolesters by both methods were excellent, as listed in Table 1 and Table 2. Compounds **25** and **26** were produced by alkylation of *S*-ethyl carbethoxythioacetate with 1 equivalent of benzyl bromide and octyl bromide, respectively, in the presence of sodium hydride (1 equivalent) using tetrahydrofuran as solvent. Compound **27**, the preparation of which will be discussed in Section 2, was converted to compound **28** by treatment with sodium ethanethiolate, prepared *in situ* from ethanethiol and sodium hydride (1:1) in tetrahydrofuran at room temperature, and to compound **29** through a

Table 1. Thiolesters from Acid Chlorides



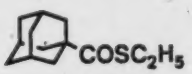
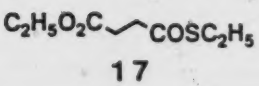
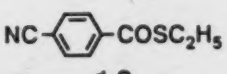
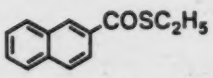
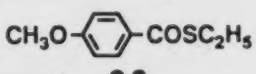
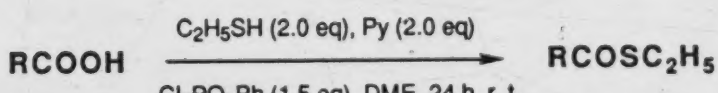
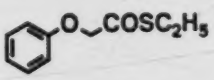
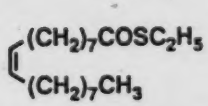
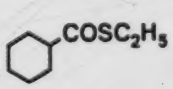
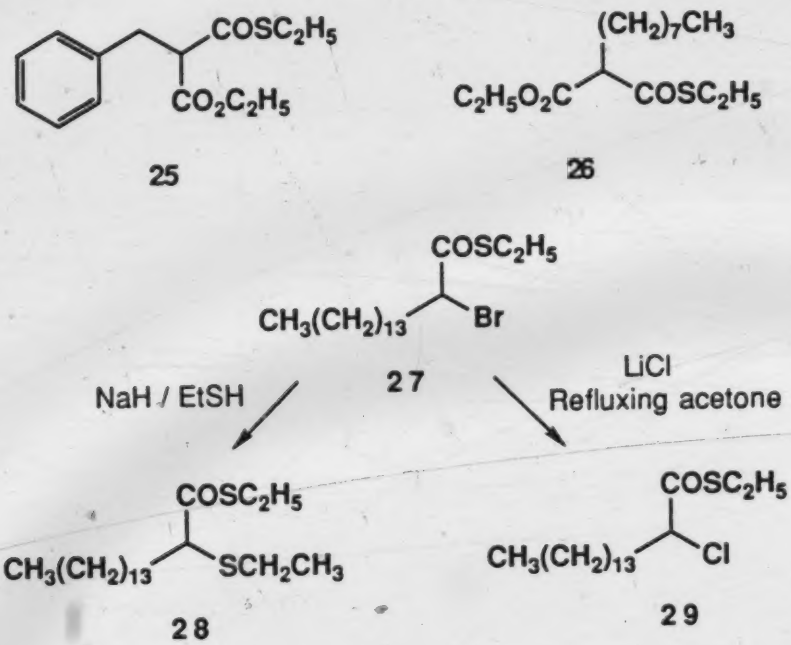
Thiolester	% Yield	Thiolester	% Yield
 **15**	100	**16**	100
 **17**	100	 **18**	100
 **19**	93	 **20**	99

Table 2. Thiolesters from Carboxylic Acids



Thiolester	% Yield	Thiolester	% Yield
 **21**	87	$CH_3(CH_2)_{16}COSC_2H_5$ **22**	86
 **23**	100	 **24**	99

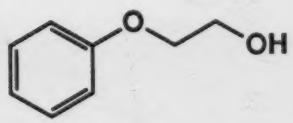
halogen exchange reaction with lithium chloride in refluxing acetone (Scheme 11). All the thiolesters used in this study were purified by flash chromatography on silica gel, and the structures were confirmed by their spectral data.



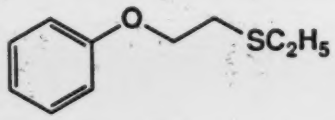
Scheme 11

For the study on the reduction reaction, compound **21** was initially treated with 1.0 molar equivalent of tetrabutylammonium borohydride in methylene chloride at room temperature. No product was observed. When the mixture was heated under reflux, the reaction proceeded slowly, resulting in the formation of compound **30** as the major product. By changing the solvent to chloroform, the reaction was much faster, but was unable to proceed to completion until the amount of the reducing

agent used was increased to 3.0 molar equivalents. When 2.5 molar equivalents of the reagent were used, the reaction did not proceed to completion even after an extended period of time and produced by-product **31** in substantial quantity.



30

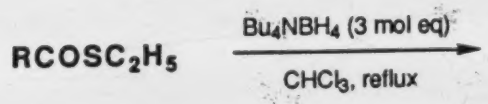


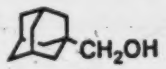
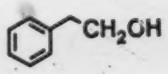
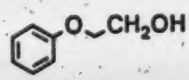
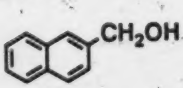
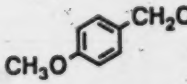
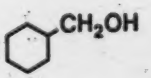
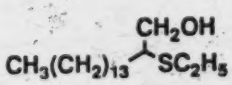
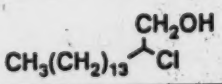
31

The ir spectrum of compound **30** showed an absorption at 3380 cm^{-1} due to the hydroxy group. The molecular ion peak at 138.0682 in the mass spectrum indicated the required molecular formula of $C_8H_{10}O_2$. In the ^1H nmr spectrum, two multiplets at δ 3.94 and 4.04 (two hydrogens each) for the ethylenyl group were observed along with a broad singlet at δ 1.72 for the hydroxy proton. Two additional multiplets at δ 6.94 (3H) and 7.30 (2H) were displayed for the aromatic protons.

The ir spectrum of compound **31** showed no absorption band for either the hydroxyl or the carbonyl group. The molecular ion peak at 128.0766 suggested its molecular formula of $C_{10}H_{14}OS$. The ^1H nmr spectrum displayed a triplet at δ 1.06 (3H) and a quartet at δ 2.47 (2H), which were coupled to each other with a coupling constant of 7 Hz, corresponding to the ethyl group. Two triplets at δ 2.72 (2H) and 4.00 (2H) with the same coupling constant of 7 Hz for the ethylenyl protons

Table 3. Reduction of Thiolesters with Tetrabutylammonium Borohydride



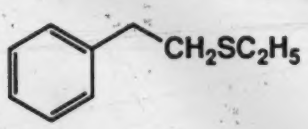
Thiolester	Time (h)	Product		% Yield [a]
15	18		32	30 (70)
16	12		33	85 (3)
21	3		30	99
22	13	$CH_3(CH_2)_{17}OH$	34	100
19	32		35	26 (73)
20	12		36	35 (58)
24	12		37	74 (10)
28	19		38	58
29	12 [b]		39	86

a. All yields given are for isolated products and have not been optimized. The number in parenthesis indicates % recovery of the starting material.

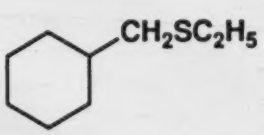
b. This reaction was performed in refluxing methylene chloride and in the presence of 2 equivalents of ethyl bromide.

were observed, along with signals at δ 6.84 (3H) and 7.22 (2H) for the phenyl group.

Under the same reaction conditions as used successfully for compound **21**, a number of thiolesters were subjected to reduction with tetrabutylammonium borohydride. The results as summarized in Table 3 show the generality of the procedure, by which the thiolester functional group is reduced to the primary alcohol. From the results, it can also be seen that the reactivities of thiolesters vary according to their structural characteristics. For example, because the presence of an α-phenoxy group significantly increases the electron deficiency of the carbonyl, compound **21** was completely reduced to the corresponding alcohol in virtually quantitative yield within 3 h. On the other hand, conjugation of the carbonyl to an aromatic ring, as in compounds **19** and **20**, substantially reduces the reactivity of the thiolester group towards the reduction. Consequently, even after long reaction times, only about 30% of the alcohols were produced along with recovery of large quantities of the unreacted thiolesters .



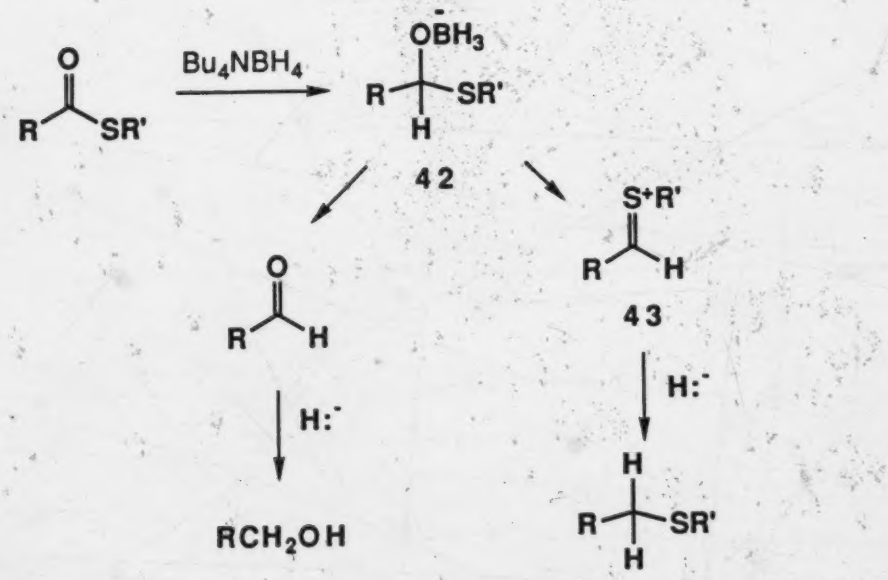
40



41

By-products similar to compound **31**, namely sulfides **40** and **41**, were also produced in small amounts (less than 13%) from the reduction of thiolesters **16** and **24**, respectively. The formation of these compounds

could be considered as a result of the overall deoxygenation of the thiolester carbonyl. The mechanism for this transformation has not been confirmed, however it is unlikely that the deoxygenation took place at the alcohol stage. More likely, it occurred at the stage of intermediate **42**, as shown in Scheme 12. After the addition of a hydride ion to the thiolester carbonyl, the resulting intermediate **42** could undergo either cleavage of the carbon-sulfur bond to form the aldehyde which was then reduced to the alcohol, or deoxygenation to give intermediate **43** from which the sulfide was formed by further reduction.



Scheme 12

The reduction of 2-chlorothiolester **29** was initially carried out in refluxing chloroform, giving a mixture of alcohols **38** and **39** in 2:3 ratio according to the ^1H nmr analysis of the mixture. Obviously, compound **38** resulted

from the replacement of the chloride with the ethyl mercaptide formed during the reaction. To suppress this undesired side reaction, the reduction was later carried out in the presence of 2.0 equivalents of ethyl bromide, which was used to trap the ethyl mercaptide. In light of the facts that the boiling point of ethyl bromide (37°C) is much lower than that of chloroform and that the reactivity of compound **29** is fairly high, chloroform was replaced with methylene chloride as a solvent. Under the modified conditions, the reaction afforded a 85% yield of compound **39**.

Selective reduction of several other multi- funtionalized thiolesters, such as compounds **17**, **18**, **23**, **25** and **26**, was attempted but without much success. From the reaction of **23**, the only identified product was a saturated alcohol which was identical to an authentic sample of 1-octadecanol (**34**). This result could be explained by invoking a concomitant reduction of the carbon-carbon double bond with borane produced under the reaction conditions. The reactions of compounds **17**, **25** and **26** gave mixtures of alcohols. The reduction of compound **18** resulted in a mixture of an alcohol and an amine, showing no selectivity at all.

2. Synthetic applications of glycidic thiolesters

It is well known that simple thiolesters are reduced to primary alcohols by Raney nickel.[27-29] However, under the influence of other funtionalities present in the molecule the thiolester group may exert some unusual

chemical properties. For example, as shown by Liu and coworkers, β-ketothiolesters and derivatives of *S,S'*-diethyl dithiomalonate underwent fragmentation reaction upon treatment with Raney nickel.[42] In light of these previous findings, it became of interest to investigate the course of reduction of glycidic thiolesters with Raney nickel.

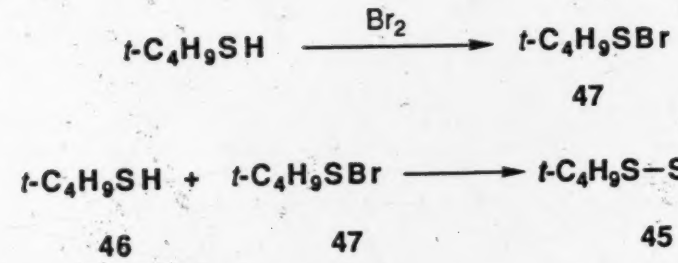
Glycidic thiolesters were first successfully prepared by Wemple and coworkers from α-bromothiolesters and carbonyl compounds.[39] α-Halothiolesters can be conveniently synthesized from mercaptans and α-halocarboxylic acids or their halides. A classical method for the preparation of the latter two kinds of compounds is by the use of Hell-Volhard-Zelinsky reaction.[50] In the presence of a catalytic amount of phosphorus tribromide, carboxylic acids possessing one or more α-hydrogens are converted to the corresponding α-bromocarboxylic acids with bromine. When more than one equivalent of phosphorus tribromide is applied, the reaction gives rise to α-bromoacyl bromide as the product. It is conceivable that the latter compound, which is unstable and difficult to handle, can be trapped with an appropriate thiol to facilitate the formation of α-bromothiolesters. On the basis of this consideration, a practical one-pot procedure has been developed for the transformation of carboxylic acids directly to α-bromothiolesters.

A. Preparation of α-bromothiolesters

The method was first demonstrated by the formation of *S-tert*-butyl 2-bromoethanethiolate (**44**) from acetic acid. A mixture of acetic acid and

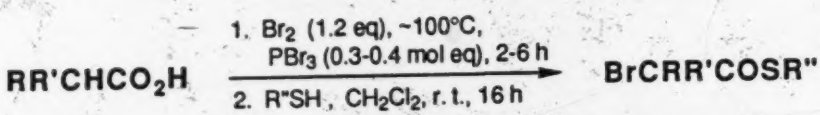
0.3 molar equivalents of phosphorus tribromide was heated in an oil bath maintained at 110°C while a small excess of bromine (1.2 equivalents) was added dropwise. The resulting brown residue was then dissolved in methylene chloride and treated with *tert*-butyl mercaptan at room temperature. The ^1H nmr spectrum of the colorless liquid thus obtained showed three singlets at δ 3.98 (2H, CH_2), 1.52 (9H, $C(CH_3)_3$) and 1.0. The last signal varied in intensity for products obtained from different runs. It was recognized that the desired product was contaminated by an impurity, possibly di-*tert*-butyl disulfide (**45**). The formation of this by-product could be due to the coupling of *tert*-butyl mercaptan (**46**) and *t*-butylsulfenyl bromide (**47**). The latter could be formed by the reaction of the former compound with the excess bromine present (Scheme 13). In order to solve this problem, a special technique was used. At the end of the bromination reaction, a stream of argon was introduced to the reaction mixture to remove unreacted bromine. Using this procedure, pure compound **44** was obtained in 89% yield.

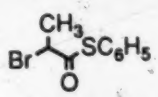
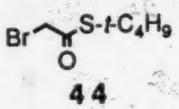
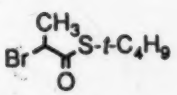
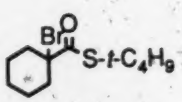
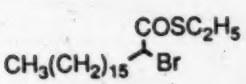
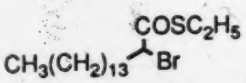
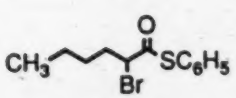
To confirm the amount of phosphorus tribromide required in the transformation, an experiment was carried out under the same conditions but using only 0.1 molar equivalent of the reagent. As a result, only 25% yield of compound **44** was obtained. Clearly a stoichiometric amount of phosphorus tribromide is required in order to obtain high yields of α-bromothiolesters. In the subsequent experiments, 0.3-0.4 molar equivalent of the reagent was used and, in all the cases examined, desired products were obtained in high yields (>80%). Results are summarized in Table 4.



Scheme 13

Table 4. α-Bromothiolesters from Carboxylic Acids



Product	% Yield	Product	% Yield
 **48**	85	 **44**	89
 **49**	91	 **50**	86
 **51**	81	 **27**	93
 **52**	91		

B. Synthesis of glycidic thiolesters

In Darzens synthesis of glycidic esters,[51] an alkoxide or sodium amide is generally used as a base. However, it is believed that a non-nucleophilic base must be applied in the synthesis of glycidic thiolesters in order to avoid nucleophilic attack on the thiolester carbonyl group by the reagent. It has also been shown[39] that α-bromothiolesters possessing a tertiary *S*-alkyl group are prefered over those with a primary or secondary *S*-alkyl group. One reason could be that the primary and secondary alkyl groups may undergo deprotonation under strongly basic conditions, as the hydrogen atom adjacent to the sulfur atom is quite acidic.[52] Another possible reason is that a thiolester derived from a tertiary mercaptan is less prone to elimination reaction leading to ketene formation. In Wemple's synthesis[39], lithium bis(trimethylsilyl)amide and sodium hydride were used as the base, and *S-tert*-butyl α-halothiolesters, including both chloro and bromo derivatives, were used as the starting material. For our investigation, a number of glycidic thiolesters were prepared from *S-tert*-butyl 2-bromoethanethiolate (**44**).

With 1.0 equivalent of lithium diisopropylamide, compound **44** was deprotonated in tetrahydrofuran at -78°C. After addition of 1.0 equivalent of dihydrocinnamaldehyde, the reaction solution was stirred at -78°C for 2 h and then warmed up to room temperature. Under these conditions, a pair of stereoisomers of compound **53** were obtained in 1:1 ratio and in a total yield of 25%. These isomeric compounds were readily separated by flash chromatography on silica gel.

The ^1H nmr spectrum of the less polar isomer displayed a nine-proton singlet at δ 1.50 for the *tert*-butyl group and a two-proton multiplet at δ 2.00 for the methylene group next to the oxirane. Signals for the benzylic protons were found at δ 2.72 and 2.83 as a pair of doublets of triplets with a large geminal coupling constant of 13 Hz. Vicinal couplings of 8 and 6 Hz were displayed respectively. A one-proton doublet of triplets at δ 3.21 and a one-proton doublet at δ 3.58, which were coupled to each other with a coupling constant of 5 Hz, were observed for the protons directly attached to the oxirane ring. A complex signal centered at δ 7.23 (5H) was due to the phenyl group. The more polar isomer displayed a similar spectrum, except that the coupling constant for the protons of the oxirane ring was only 1.5 Hz, much smaller than that observed for the less polar isomer. Accordingly,[53] the stereochemistry of the less polar isomer and the more polar isomer was assigned as *cis*, and *trans*, respectively.

In order to improve the yield, several runs of the reaction were carried out using increasing amounts of thiolester **44** and lithium diisopropylamide. With 2.5 equivalents each of **44** and the base, a 62% yield (based on the aldehyde) of glycidic thiolesters **53** was obtained. This yield could not be further improved by the use of an even greater amount of thiolester **44**.

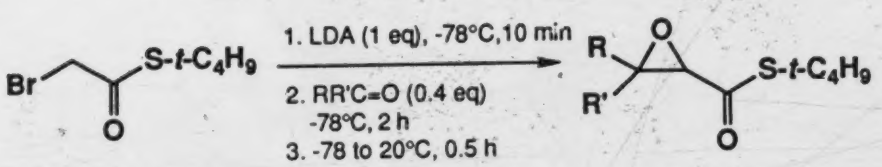
It appears that the excess amount of thiolester **44** was required in order to cover its rapid consumption due to side reactions such as self-condensation. In a control experiment, thiolester **44** was treated with

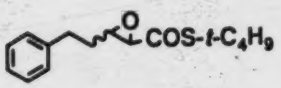
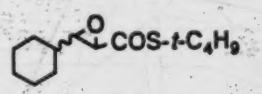
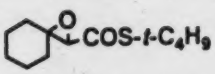
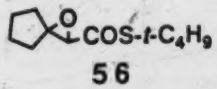
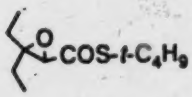
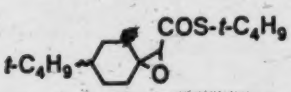
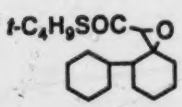
lithium diisopropylamide (1 equivalent) at -78°C in tetrahydrofuran for 2 h. The mixture was then allowed to warm up to room temperature (*ca.* 0.5 h). A substantial loss of material occurred and less than 60% of the starting thiolester **44** was recovered.

In the subsequent preparation of glycidic thiolesters, the following standard procedure was adopted. The enolate ion of thiolester **44** was preformed by treatment with lithium diisopropylamide (1 equivalent) in tetrahydrofuran at -78°C for 10 min. The carbonyl compound (0.4 equivalent) was then introduced. After 2 h at -78°C, the reaction mixture was warmed to room temperature (*ca.* 0.5 h). Under these conditions, several glycidic thiolesters were prepared in modest yields of 62-85%. The results are summarized in Table 5.

Similar to Darzens synthesis of glycidic esters, the formation of glycidic thiolesters is expected to proceed *via* the following three steps: deprotonation of an α-halothiolester, nucleophilic addition of the enolate ion thus formed to a carbonyl compound, and cyclization to form the oxirane ring (Scheme 14). It was observed during the preparation of compound **53** that an intermediate was produced immediately following the addition of dihydrocinnamaldehyde at -78°C. This intermediate was slowly (*ca.* 5 h) converted to the desired product at low temperature (-78°C). This observation also indicated that the final cyclization was much slower than the addition of the enolate anion to the carbonyl compound.

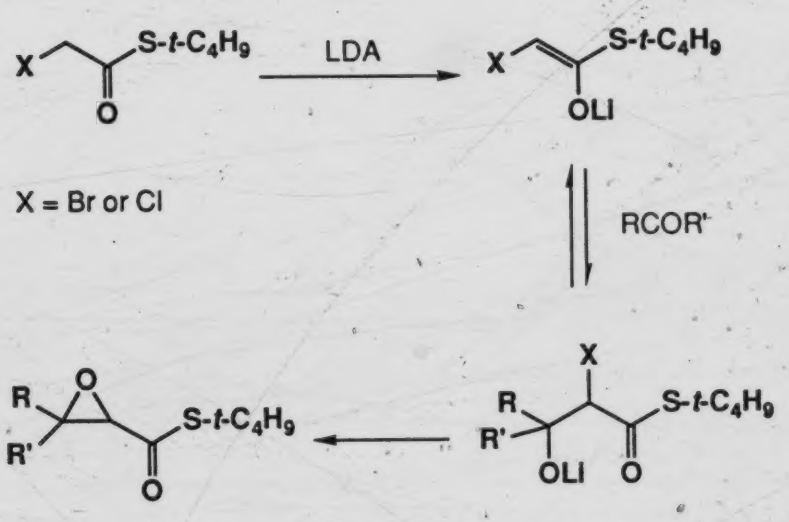
Table 5. Preparation of Glycidic Thiolesters



Glycidic Thiolester	% Yield	Glycidic Thiolester	% Yield
 **53**	62 (*cis* /*trans* 1:1)	 **54**	85 (*cis* /*trans* 1:1)
 **55**	83	 **56**	81
 **57**	66	 **58**	78 (*cis* /*trans* 2:1)
 **59**	70 (mixture of isomers)		

We have also examined the condensation of *S-tert*-butyl 2–chloroethanethioate (**60**) with carbonyl compounds. This reagent was found to be inferior to the corresponding bromo compound. At -78°C over a period of 5 h, the reaction of its enolate ion with cyclohexanone gave rise to alcohol **61** as the only product in 81% yield. When the reaction was carried out by slowly warming the reaction mixture to room temperature over a 2.5 h period, the desired product **55** was formed but in poor yield of 19%. Similarly, the condensation of **60** with

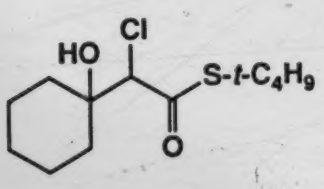
dihydrocinnamaldehyde at -78°C gave alcohol **62** as the only product (38% yield). In this case, the formation of the desired product **53** was not detected even after the reaction temperature was raised to 20°C.



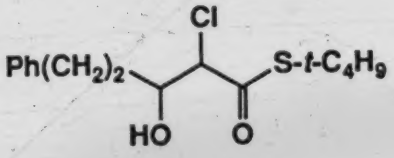
Scheme 14

The ir spectrum of compound **62** showed hydroxy and carbonyl absorption bands at 3400 and 1660 cm^{-1}, respectively. In the ^1H nmr spectrum, signals for *tert*-butyl and phenyl protons were displayed at δ 1.37 (s, 9H) and 7.25 (m, 5H). Two complex signals at δ 1.8-2.1 (2H) and 2.65 (2H) were observed for the ethylenyl group, along with a broad singlet at δ 2.5 (1H) for the hydroxy proton. Two one-proton signals, a doublet at δ 4.27 and a multiplet at δ 4.07, were displayed for the protons α- and β- to the carbonyl, respectively. Similarly, the ir spectrum of compound **61** showed absorption bands at 3500, 1689 and

1664 cm^{-1}. In the ^1H nmr spectrum, two singlets at δ 4.16 (1H) and 1.50 (9H) were observed for the α-proton and the *tert*-butyl group.



61



62

Treatment of compounds **61** or **62** with a base such as sodium hydride in tetrahydrofuran or dimethoxyethane at room temperature did not yield any detectable amount of the desired glycidic thiolester. Instead, complete decomposition to give original components, α-chlorothiolester and the carbonyl compound, occurred.

The above results clearly indicated that α-chlorothiolester is not an adequate reagent for the preparation of glycidic thiolesters *via* Darzens condensation. This is in agreement with the previous findings made by Wemple and coworkers.[39] The isolation of intermediate chloro alcohols **61** and **62** and the observed reverse reaction of these intermediates lend support to the proposed mechanistic pathway depicted in Scheme 14.

C. Reduction of glycidic thiolesters with Raney nickel

Glycidic thiolester *cis*-**53** was treated with W-2 Raney nickel in 95% ethanol at room temperature for 1 h. After filtration and concentration of

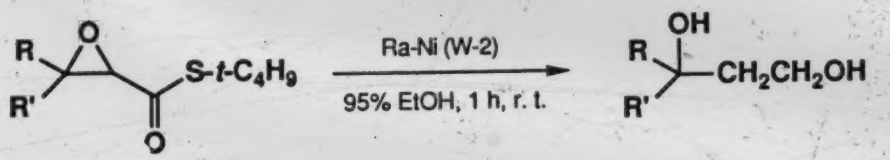
the filtrate, diol **63** was obtained. The mass spectrum revealed its molecular formula to be $C_{11}H_{16}O_2$. The ir spectrum indicated the presence of a hydroxy group showing a strong absorption at 3343 cm^{-1}. This was also confirmed by the signal at δ 2.3 for two D_2O exchangeable hydrogens in the ^1H nmr spectrum. However, at this stage the relationship (i.e.1,2- or 1,3-) of the two hydroxy groups could not be determined by the ^1H nmr spectrum due to the complexity of the signal at δ 3.8-4.0 for the three hydrogens adjacent to the hydroxy groups.

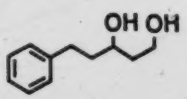
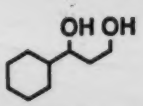
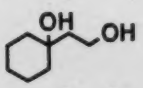
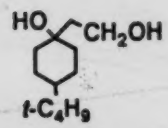
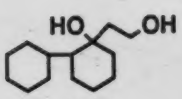
To solve this problem, the diol was converted to the corresponding diacetate by treatment with excess acetic anhydride and pyridine in methylene chloride. The ^1H nmr spectrum clearly indicated that the product was a 1,3-diacetate derived from 1,3-diol **63**, displaying two low-field signals, a triplet at δ 4.10 (J = 6.5 Hz) for two hydrogen atoms and a triplet of triplets at δ 5.04 (J = 7, 5.5 Hz) integrating to one hydrogen.

Similar treatment of glycidic thiolesters **54**, **55**, **58** and **59** with Raney nickel gave rise to 1,3-diols **64**, **65**, **66** and **67** respectively. An examination of the results compiled in Table 6 reveals that the reduction in each case proceeded in a completely regioselective manner with preferential cleavage of the carbon-oxygen bond neighboring the thiolester group. As such this bond is expected to be activated by the electron-withdrawing thiolester group. Furthermore, in compounds **55**, **58**, and **59**, this bond happens also to be sterically less congested than the other carbon-oxygen bond of the oxirane ring. Most likely, it is the

combination of these electronic and steric effects which induced the observed high degree of regioselectivity.

Table 6. Reduction of Glycidic Thiolesters with Raney Nickel



Entry	Thiolester	Product	% Yield
1	*cis*-**53**	 **63**	80
2	**54** (isomeric mixture)	 **64**	88
3	**55**	 **65**	87
4	**58** (*cis*:*trans* = 1:2)	 **66** (*cis*:*trans* = 1:2)	80
5	**59** (isomeric mixture)	 **67**	96

D. Reduction of glycidic thiolesters with sodium borohydride and lithium aluminum hydride

Thiolesters have been shown to be more susceptible to reduction with metal hydride reducing agents than the corresponding oxygen analogue and could be reduced to the alcohol level under mild conditions with sodium borohydride in protic solvents[36] and tetrabutylammonium borohydride in aprotic solvents (*vide supra*). It has also been shown that a clear differentiation of the thiolester group from other frequently encountered acid derivatives, namely ester, amide and nitrile, could be achieved using sodium borohydride.

In this part of the study, several glycidic thiolesters were subjected to sodium borohydride reduction in order to investigate the viability to reduce the thiolester group selectively without affecting the adjacent epoxy ring. This study was carried out with the intention to expand the synthetic scope of Darzens glycidic thiolester synthesis to the preparation of 2,3-epoxy alcohols. Thus, compound **55** was treated with 4.0 molar equivalents of sodium borohydride in 98% ethanol at 20°C. The reduction was found to be completed within 5 h. The usual work-up of the reaction followed by flash chromatography of the crude product on silica gel gave compound **68** in 82% yield. The structure of **68** was confirmed by its spectral data and elemental analysis. The mass spectrum indicated the molecular formula of $C_8H_{14}O_2$, which was also confirmed by the elemental analysis. The ir spectrum showed an

absorption at 3400 cm^{-1} for the hydroxy group. In the ^1H nmr spectrum, there were signals at δ 3.00 (dd, 1H, J = 7, 4.5 Hz) for the hydrogen on the oxirane ring, δ 3.70 (ddd, 1H, J = 12, 7, 4.5 Hz) and 3.81 (ddd, 1H, J = 12, 9, 4.5 Hz) for the hydrogens attached to the carbon bearing the hydroxy group.

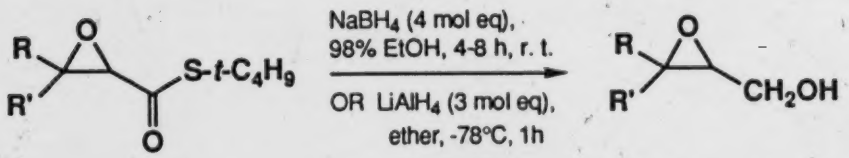
This procedure is apparently general for the selective reduction of glycidic thiolesters. Under similar conditions, compounds *trans*-**53**, *cis*-**53**, *cis*-**54** and **59** were also smoothly reduced to their corresponding epoxy alcohols in good yields of 80-95%. Results are compiled in Table 7.

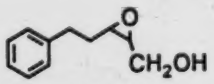
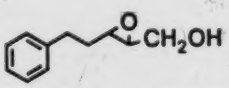
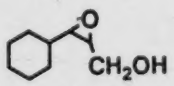
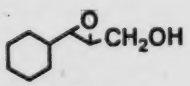
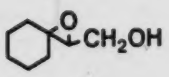
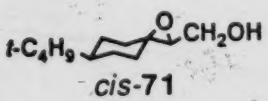
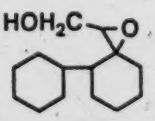
It should be noted that up to 4.0 molar equivalents of the reducing agent was required for completion of the reaction presumably because of the consumption of the reagent by the solvent. The amount could be reduced to 2.5 molar equivalents by addition of the reagent in portions (0.5 molar equivalent over every 0.5 h period) during the reaction.

The formation of epoxy alcohols from glycidic thiolesters can also be achieved by the use of lithium aluminum hydride at low temperature. For example, when compound *trans*-**54** was treated with 3.0 molar equivalents of the reducing agent in ethyl ether at -78°C for 1 h, epoxy alcohol *trans*-**70** was obtained in 89% yield. The presence of hydroxy group was evident from the absorption band at 3418 cm^{-1} in the ir spectrum. The required molecular formula of $C_9H_{16}O_2$ was confirmed by

Table 7. Reduction of Glycidic Thiolesters

with Sodium Borohydride and Lithium Aluminum Hydride



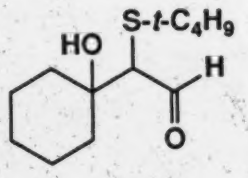
Thiolester	Product	% Yield with $NaBH_4$	% Yield with $LiAlH_4$
cis-53	 *cis*-69	94	94
trans-53	 *trans*-69	80	
cis-54	 *cis*-70	90	83
trans-54	 *trans*-70		89
55	 68	82	
cis-58	 *cis*-71		92
59 (isomeric mixture)	 72 (isomeric mixture)	95	86

the molecular ion peak at 174.11 in the chemical ionization mass spectrum induced by ammonia. In the ^{1}H nmr spectrum, an intense complex signal at δ 1.0-2.0 was displayed for the hydroxy proton and eleven cyclohexyl protons. Signals for the oxirane protons were shown at δ 2.80 and 3.03, which were coupled to each other with a small coupling constant of 2.5 Hz, indicating retention of the *trans* configuration. The later signal (δ 3.03) was also coupled with signals at δ 3.67 (J = 4 Hz) and 3.95 (J = 2.5 Hz) for the protons of the hydroxymethyl group. The geminal coupling constant between these two methylene protons was found to be 12 Hz.

The reduction was also attempted using 1.0 molar equivalent of lithium aluminum hydride. At -78°C, the reaction was found to be slow and incomplete after a long time of reaction. When the reaction was carried out at room temperature, a complex mixture was produced, from which one compound was isolated in 5% yield. This compound was identified as hydroxy aldehyde **73** on the basis of the following spectral data. The ir spectrum showed absorption bands at 3480 and 1700 cm^{-1}, characteristic of hydroxy and carbonyl groups, respectively. In the ^{1}H nmr spectrum, two one-proton doublets at δ 9.5 and 3.1, which were coupled to each other, were observed for the aldehydic proton and the neighboring methine proton. A nine-proton singlet at δ 1.1 was due to the *tert*-butyl group. A one-proton singlet at δ 2.1 was displayed for the hydroxy group, and an intense complex signal at δ 1.5-1.6 could be attributed to the ten protons attached to the cyclohexyl ring. Compound **73** was obviously produced as a result of the epoxy ring opening with

tert-butyl mercaptide formed during the reduction. It appears that at higher temperature the cleavage of the epoxy ring induced by various nucleophiles, such as *tert*-butyl mercaptide, hydride and alkoxide (reduction product), led to the formation of the complex mixture.

Several other glycidic thiolesters were subjected to reduction with a large excess (3 molar equivalents) of lithium aluminum hydride at low temperature (-78°C). As indicated by the results outlined in Table 7, these conditions are generally effective for the selective reduction of the thiolester group.



73

3. Conclusion

Several new synthetic aspects of thiolesters were explored. It was found that reduction of the thiolester group could be effected in aprotic solvent using tetrabutylammonium hydride as a reducing agent. Reduction of glycidic thiolesters, readily prepared by an α-bromo thiolester version of the Darzens glycidic ester condensation, with Raney nickel was shown to give consistently the corresponding 1,3-diols as a result of the completely regioselective cleavage of the epoxy ring. On the other hand, with sodium borohydride at room temperature or lithium aluminum hydride at

-78°C, glycidic thiolesters were readily reduced to give 2,3-epoxy alcohols resulting from the chemoselective reduction of the thiolester moiety. During the course of these studies, a convenient general method for the preparation of α-bromo thiolesters has been developed based on the trapping, with thiol, of the unstable α-bromoacyl bromide produced by Hell-Volhard-Zelinsky reaction.

EXPERIMENTAL

General

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer. Unless otherwise stated, ir samples were run as thin films. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-80, Bruker WH-200 or Bruker WH-400 spectrometer and, except where otherwise stated, were obtained on solutions in deuterochloroform with tetramethylsilane as internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, bs = broad singlet, and br = broad. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometers. Concentrations of solvent systems used in column chromatography are given by volumes.

Materials

Chloroform used for reactions was washed eight times with water, dried over and distilled from anhydrous magnesium sulfate. Methylene chloride was distilled from anhydrous magnesium sulfate. Ethyl ether, 1,2-dimethoxyethane and tetrahydrofuran were distilled from sodium metal and benzophenone under an argon atmosphere. Ethyl acetate,

hexane, ether and methylene chloride used for chromatography and extraction were purified by distillation. Argon was passed through a purification train of Fieser's solution, concentrated sulfuric acid, and potassium hydroxide pellets. Silica gel, 230-400 mesh ASTM, was used as absorbent for flash chromatography. Thin-layer chromatography was carried out using Merck TLC aluminum sheets silica gel 60 F_{254}. Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Commercially available bromine was used without further purification.

Reduction of thiolester with tetrabutylammonium borohydride

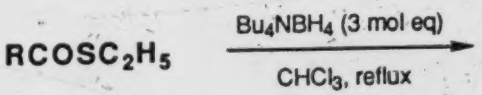
To a solution of thiolester **21** (0.214 g, 1.09 mmol) in chloroform (10 mL) under an argon atmosphere, was added tetrabutylammonium borohydride (0.843 g, 3.28 mmol). The reaction mixture was heated under reflux for 3 h, cooled to room temperature, and carefully acidified with aqueous 1 *N* hydrochloric acid (3 mL). The resulting mixture was poured into ice-cold aqueous 1 *N* sodium hydroxide solution (30 mL) and extracted with methylene chloride. The extracts were washed with aqueous sodium chloride solution, dried, filtered and concentrated. The residue was subjected to column chromatography on silica gel. Elution with ethyl acetate-hexane (4:6) gave 2-phenoxyethanol (**30**) (0.149 g, 99% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.72 (bs, 1H, -O**H**), 3.94 (m, 2H, -C**H**$_2$OH), 4.04 (m, 2H, -C**H**$_2$OPh), 6.94 (m, 3H, *o*, *p*-Ar**H**), and 7.30 (complex, 2H, *m*-Ar**H**); ir 3380 cm^{-1} (OH); ms M$^+$ 138.0682 (calcd. for $C_8H_{10}O_2$: 138.0680).

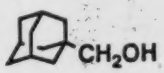
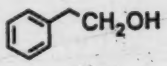
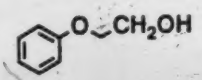
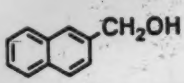
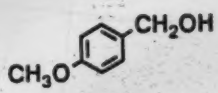
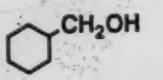
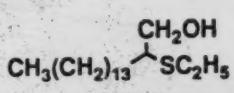
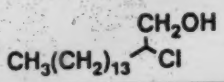
A parallel experiment was carried out under similar reaction conditions using methylene chloride as a solvent. After refluxing for 5 h, the reaction mixture was worked up as before to give 48% yield of **30** and 34% recovery of the starting thiolester **21**.

In another experiment, tetrabutylammonium borohydride (0.643 g, 2.50 mmol) was added to a solution of **21** (0.198 g, 1.00 mmol) in chloroform (10 mL) under an argon atmosphere. The reaction mixture was heated under reflux for 17 h, cooled to room temperature, and carefully acidified with aqueous 1 *N* hydrochloric acid (3 mL). The resulting mixture was poured into ice-cold aqueous 1 *N* sodium hydroxide solution (30 mL) and extracted with methylene chloride. The extracts were washed with aqueous sodium chloride solution, dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with ethyl acetate-hexane (4:6) gave **30** (0.084 g, 64% yield). Further elution with ethyl acetate-hexane (1:9) gave 1-ethylthio-2-phenoxyethane (**31**, 0.058 g, 32% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7 Hz, -CH_2CH_3), 2.39 (q, 2H, J = 7 Hz, -CH_2CH_3), 2.72 (t, 2H, J = 7 Hz, -CH_2CH_2S-), 4.00 (t, 2H, J = 7 Hz, -OCH_2-), 6.84 (m, 3H, Ar**H**), and 7.22 (m, 2H, Ar**H**); ir no absorption for OH or C=O; ms M^+ 182.0766 (calcd. for $C_{10}H_{14}OS$: 182.0765).

According to the first experiment described above, the following thiolesters were heated under reflux with 3.0 molar equivalents of tetrabutylammonium borohydride in chloroform for 12-30 h to form the

Table 3. Reduction of Thiolesters with Tetrabutylammonium Borohydride



Thiolester	Time (h)	Product		% Yield [a]
15	18		**32**	30 (70)
16	12		**33**	85 (3)
21	3		**30**	99
22	13	$CH_3(CH_2)_{17}OH$	**34**	100
19	32		**35**	26 (73)
20	12		**36**	35 (58)
24	12		**37**	74 (10)
28	19		**38**	58
29	12 [b]		**39**	86

a. All yields given are for isolated products and have not been optimized. The number in parenthesis indicates % recovery of the starting material.

b. This reaction was performed in refluxing methylene chloride and in the presence of 2 equivalents of ethyl bromide.

corresponding alcohols (30-100% yields). The reaction time used and the yield obtained for each case are shown in Table 3.

***S*-Ethyl 1-adamantanecarbothioate (15)** gave 1-adamantylmethanol (**32**): mp 106-110°C; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.32 (bs, 1H, -O**H**), 1.62-2.00 (complex, 15H), and 3.19 (s, 2H, -C**H**$_2$OH); ir 3220 cm^{-1} (OH); ms M$^+$ 166.1358 (calcd. for $C_{11}H_{18}O$: 166.1358).

***S*-Ethyl 2-phenylethanethioate (16)** gave 2-phenylethanol (**33**): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.80 (bs, 1H, -O**H**), 2.86 (t, 2H, J = 7 Hz, PhC**H**$_2$-), 3.82 (t, 2H, J = 7 Hz, -C**H**$_2$OH), and 7.2-7.4 (complex, 5H, Ar**H**).

***S*-Ethyl octadecanethioate (22)** gave 1-octadecanol (**34**): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 6.5 Hz, -CH$_2$C**H**$_3$), 1.30 (complex, 30H), 1.58 (complex, 3H, -O**H** and -CH$_2$C**H**$_2$OH), and 3.68 (t, 2H, J = 7 Hz, -C**H**$_2$OH); ir 3350 cm^{-1} (OH).

***S*-Ethyl 2-naphthalenecarbothioate (19)** gave 2-hydroxymethylnaphthalene (**35**): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.82 (bs, 1H, -O**H**), 4.86 (d, 2H, J = 4 Hz, -C**H**$_2$OH), and 7.44-7.58 (complex, 7H, Ar**H**); ir 3270 cm^{-1} (OH); ms M$^+$ 158.0732 (calcd. for $C_{11}H_{10}O$: 158.0732).

***S*-Ethyl 4-methoxylbenzenecarbothioate (20)** gave 4-methoxyphenylmethanol (**36**): ^{1}H nmr (80 MHz, $CDCl_3$) δ 1.80 (bs, 1H, -O**H**), 3.80 (s, 3H, -OC**H**$_3$), 4.60 (s, 2H, -C**H**$_2$OH), 6.93 (d, 2H, J = 8 Hz, Ar**H**),

and 7.30 (d, 2H, J = 8 Hz, ArH); ir 3360 cm^{-1} (OH); ms M^+ 138.0681 (calcd. for $C_8H_{10}O_2$: 138.0681).

***S*-Ethyl cyclohexanecarbothioate (24)** gave cyclohexylmethanol (**37**): ^1H nmr (200 MHz, $CDCl_3$) δ 0.85-1.90 (complex, 11H), 2.10 (bs, 1H, -OH), and 3.51 (d, 2H, J = 6.5 Hz, $-CH_2OH$); ir 3329 cm^{-1} (OH); ms M^+ 114.1044 (calcd. for $C_7H_{14}O$: 114.1044).

***S*-Ethyl 2-ethylthiohexadecanethioate (28)** gave 2-ethylthiohexadecan-1-ol (**38**): ^1H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 6.5 Hz, $-CH_3$), 1.2-1.6 (complex, 29H), 2.50 (bs, 1H, -OH), 2.55 (q, 2H, J = 7.5 Hz, $-SCH_2-$), 2.75 (m, 1H, -SCH-), 3.52 (m, 1H, -CHHOH), and 3.67 (m, 1H, -CHHOH).

Reduction of *S*-Ethyl 2-chlorohexadecanethioate (29)

To a solution of thiolester **29** (0.159 g, 0.475 mmol) in methylene chloride (10 mL) under an argon atmosphere, were added ethyl bromide (0.103 g, 0.950 mmol) and tetrabutylammonium borohydride (0.366 g, 1.425 mmol). The reaction mixture was heated under reflux for 12 h, cooled to room temperature, and carefully acidified with aqueous 1 N hydrochloric acid (3 mL). The resulting mixture was poured into ice-cold aqueous 1 N sodium hydroxide solution (30 mL) and extracted with methylene chloride. The extracts were washed with aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The residue was subjected to column chromatography on silica gel.

Elution with ethyl acetate-hexane (4:6) gave 2-chloro-1-hexadecanol (**39**, 0.114 g, 0.411 mmol, 86% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7 Hz, -C**H**$_3$), 1.2-1.8 (complex, 26H), 2.60 (bs, 1H, -O**H**), 3.66 (dd, 1H, *J* = 12, 7 Hz, -C**H**HOH), 3.74 (dd, 1H, *J* = 12, 4 Hz, -CH**H**OH), and 3.99 (m, 1H, -C**H**Cl-); ir 3375 cm^{-1} (OH). Acetylation of **39** with acetic anhydride and pyridine in methylene chloride gave 2-chloro-1-hexadecyl acetate: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 6.5 Hz, -CH$_2$C**H**$_3$), 1.2-1.4 (complex, 24H), 1.85 (m, 2H, -C**H**$_2$CH$_3$), 2.12 (s, 3H, -COC**H**$_3$), 4.09, (m, 1H, -C**H**Cl-), 4.23 (dd, 1H, *J* = 11, 6 Hz, -C**H**HO-), and 4.25 (dd, 1H, *J* = 11, 6 Hz, -CH**H**O-); ms M$^+$ 320.2296 and 318.2317 (calcd. for $C_{18}H_{35}ClO_2$: 320.2296 and 318.2325).

S-Phenyl 2-bromopropanethioate (48)

A mixture of propionic acid (3.70 g, 50 mmol) and phosphorus tribromide (3.24 g, 20 mmol) was placed in a three-neck flask equipped with a dropping funnel, a magnetic stirrer and a condenser connecting to a hydrogen bromide gas absorption bottle containing aqueous sodium hydroxide solution. While the mixture was heated by an oil-bath maintained at 100-120°C, liquid bromine (3.1 mL, 60 mmol) was added dropwise over a period of 1.5 h. The completion of the reaction was indicated by the retention of the brown color of bromine. The system was then flushed with a moderate flow of argon to remove excess bromine (*ca.* 0.5 h). When the color of the reaction mixture turned to light yellow, the oil bath was removed and methylene chloride (20 mL) was introduced. After the reaction mixture was cooled to room temperature, a

solution of thiophenol (5.78 g, 52.5 mmol) in methylene chloride (20 mL) was slowly added. After stirring for 16 h, the mixture was washed with saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The organic solutions were washed with aqueous saturated sodium chloride solution, combined, dried (Na_2SO_4), filtered and concentrated. Vacuum distillation (108-112°C / 0.1 mmHg) of the residue gave compound **48** (10.4 g, 42 mmol, 85% yield): ^{1}H nmr (80 MHz, $CDCl_3$) δ 1.90 (d, 3H, J = 7 Hz, -C**H**$_3$), 4.62 (q, 1H, J = 7 Hz, -C**H**Br-), and 7.45 (s, 5H, Ar**H**); ir 1705 cm^{-1} (C=O); ms M$^+$ 245.9531 and 243.9552 (calcd. for C_9H_9BrOS: 245.9537 and 243.9558). Anal. Calcd. for C_9H_9BrOS: C, 44.10; H, 3.70; S, 13.08. Found: C, 44.42; H, 3.67; S, 13.32.

Preparation of other 2-bromothiolesters

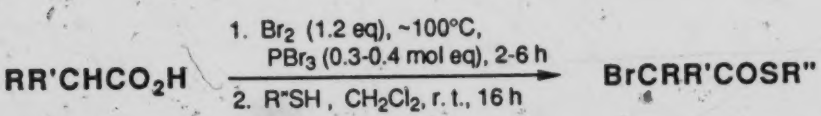
Using the procedure illustrated above with compound **48**, α-bromothiolesters **27**, **44**, **49-52** were prepared from the corresponding carboxylic acids and thiols. Yields of products are compiled in Table 4.

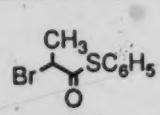
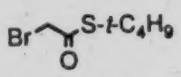
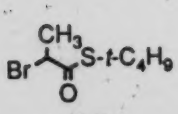
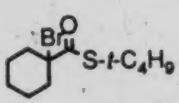
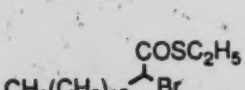
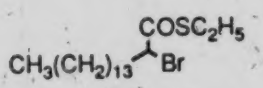
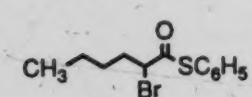
***S-tert*-Butyl 2-bromoethanethioate (44)**: bp. 80-84°C / 11 mmHg; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.52 (s, 9H, -C(C**H**$_3$)$_3$), and 3.98 (s, 2H, -C**H**$_2$-); ir 1690 and 1670 cm^{-1} (C=O); ms M$^+$ 211.9742 and 209.9714 (calcd. for $C_6H_{11}BrOS$: 211.9693 and 209.9714).

***S-tert*-Butyl 2-bromopropanethioate (49)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $-C(CH_3)_3$), 1.75 (d, 3H, J = 7 Hz, $-CH_3$), and 4.40 (q, 1H, J = 7 Hz, -CHBr-).

***S-tert*-Butyl 1-bromocyclohexanecarbothioate (50)**: bp 80-85°C / 0.1 mmHg; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $-C(CH_3)_3$), and 1.2-2.3 (complex, 10H); ir 1672 cm^{-1} (C=O); ms M^+ 280.0314 and 278.0334 (calcd. for $C_{11}H_{19}BrOS$: 280.0319 and 278.0340).

Table 4. α-Bromothiolesters from Carboxylic Acids



Product	% Yield	Product	% Yield
 **48**	85	 **44**	89
 **49**	91	 **50**	86
 **51**	81	 **27**	93
 **52**	91		

***S*-Ethyl 2-bromooctadecanethioate (51)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7 Hz, -CH_3), 1.2-1.6 (complex, 28H), 1.30 (t, 3H, J = 7.5 Hz, -SCH_2CH_3), 1.95-2.15 (m, 2H, -CH_2CHBr-), 2.99 (q, 2H, J = 7.5 Hz, -SCH_2CH_3), and 4.42 (dd, 1H, J = 8, 7 Hz, -CHBr-); ms (CI) $(M + NH_4)^+$ 426 and 424 (calcd. for $C_{20}H_{43}BrNOS$: 426 and 424).

***S*-Ethyl 2-bromohexadecanethioate (27)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7 Hz, -CH_3), 1.2-1.6 (complex, 24H), δ 1.32 (t, 3H, J = 7.5 Hz, -SCH_2CH_3), 1.98-2.26 (m, 2H, -CH_2CHBr-), 3.01 (q, 2H, J = 7.5 Hz, -SCH_2CH_3), and 4.46 (dd, 1H, J = 8, 7 Hz, -CHBr-).

***S*-Phenyl 2-bromohexanothioate (52)**: bp 130-140°C / 0.05 mmHg; ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz, -CH_3), 1.3-1.6 (complex, 4H), 2.0-2.3 (m, 2H, -CH_2CHBr-), 4.53 (dd, 1H, J = 7, 7 Hz, -CHBr-), and 7.52 (s, 5H, ArH); ir 1705 cm^{-1} (C=O); ms M^+ 288.0010 and 286.0021 (calcd. for $C_{12}H_{15}BrOS$: 288.0006 and 286.0027).

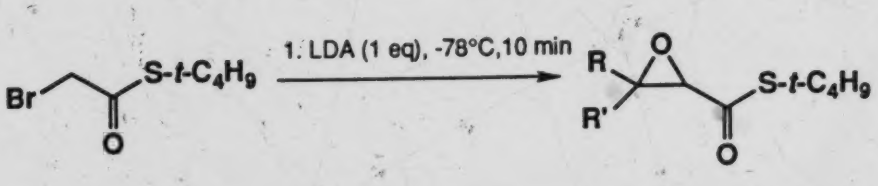
Preparation of glycidic thiolesters

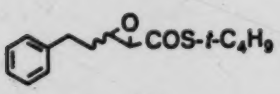
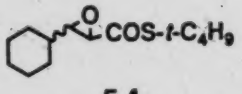
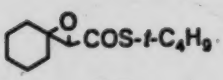
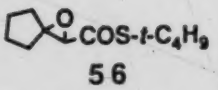
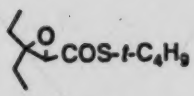
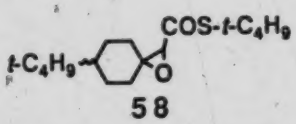
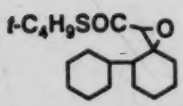
A number of glycidic thiolesters were synthesized from compound **44** and the carbonyl compounds. A typical experimental procedure is given below with compound **53**. The yield for each product is shown in Table 5.

***S*-*tert*-Butyl 3-(2-phenylethyl)oxirane-2-carbothioate (53)**

Under an argon atmosphere , diisopropylamine (1.11 g, 11.0 mmol) and tetrahydrofuran (30 mL) were placed in a flask and cooled to -78°C by a dry ice-acetone bath. A 2.0 *M* butyllithium solution in hexane (5.0 mL, 10.0 mmol) was slowly added with a syringe. After stirring for 10 min, a solution of compound **44** (2.11 g, 10.0 mmol) in tetrahydrofuran (5.0 mL) was added dropwise over a period of 10 min. Then a solution of dihydrocinnamaldehyde (0.536 g, 4.00 mmol) in tetrahydrofuran (5.00 mL) was added dropwise. The resulting mixture was stirred at -78°C for 2 h and the cooling bath was removed. After the mixture was warmed up to room temperature, it was poured into an aqueous ammonium chloride solution and extracted with ethyl ether (3 x 20 mL). The extracts were washed with aqueous saturated sodium chloride solution, combined, dried, filtered and concentrated to give a brown oil. Flash chromatography of the residue (2-15% ethyl ether in hexane) gave *cis*-**53** (0.345 g, 1.31 mmol) and *trans*-**53** (0.310 g, 1.17 mmol). *cis*-**53**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, -C(C**H**$_3$)$_3$), 2.00 (m, 2H, -C**H**$_2$C**H**$_2$Ph), 2.74 (dt, 1H, *J* = 13, 8 Hz, -C**H**HPh), 2.83 (dt, 1H, *J* = 13, 6 Hz, -CH**H**Ph), 3.21 (dt, 1H, *J* = 5, 6 Hz, -CH$_2$C**H**-), 3.58 (d, 1H, *J* = 5 Hz, -C**H**CO-), and 7.30 (complex, 5H, Ar**H**). *trans*-**53**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, -C(C**H**$_3$)$_3$), 1.92 (m, 2H, -C**H**$_2$C**H**$_2$Ph), 2.77 (ddd, 1H, *J* = 13, 9, 4 Hz, -C**H**HPh), 2.80 (ddd, 1H, *J* = 13, 8.5, 4 Hz, -CH**H**Ph), 3.19 (ddd, 1H, *J* = 6.5, 6, 2 Hz, -CH$_2$C**H**-), 3.26 (d, 1H, *J* = 2 Hz, -C**H**CO-), and 7.23 (complex, 5H, Ar**H**); ir 1670 cm^{-1} (C=O) ; ms (CI) $(M + NH_4)^+$ 282.11 (calcd. for $C_{15}H_{24}NO_2S$: 282.15).

Table 5. Preparation of Glycidic Thiolesters



Glycidic Thiolester	% Yield	Glycidic Thiolester	% Yield
 **53**	62 (*cis* /*trans* 1:1)	 **54**	85 (*cis* /*trans* 1:1)
 **55**	83	 **56**	81
 **57**	66	 **58**	78 (*cis* /*trans* 2:1)
 **59**	70 (mixture of isomers)		

***S-tert*-Butyl 3-cyclohexyloxirane-2-carbothioates (54)** ***trans*-54**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.48 (s, 9H, -C(CH_3)$_3$), 1.1-1.95 (complex, 11H), 2.98 (dd, 1H, J = 6.5, 2 Hz, -CH_2CHCO-), and 3.33 (d, 1H, J = 2 Hz, -CHCO-). ***cis*-54**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.51 (s, 9H, -C(CH_3)$_3$), 1.1-1.9 (complex, 11H), 2.95 (dd, 1H, J = 9 , 4.5 Hz, -CH-), and 3.61 (d, 1H, J = 4.5 Hz, -CHCO-); ms M^+ 242.1327 (calcd. for $C_{13}H_{22}O_2S$: 242.1340).

***S-tert*-Butyl 1-oxaspiro[2.5]octane-2-carbothioate (55)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $-C(CH_3)_3$), 1.5-1.8 (complex, 10H), and 3.36 (s, 1H, -CHCO-); ir 1695 and 1667 cm^{-1} (C=O); ms M^+ 228.1183 (calcd. for $C_{12}H_{20}O_2S$: 228.1184).

***S-tert*-Butyl 1-oxaspiro[2.4]heptane-2-carbothioate (56)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.50 (s, 9H, $-C(CH_3)_3$), 1.6-2.1 (complex, 8H), and 3.57 (s, 1H, -CHCO-); ir 1693 and 1668 cm^{-1} (C=O); ms M^+ 214.1022 (calcd. for $C_{11}H_{18}O_2S$: 214.1027).

***S-tert*-Butyl 3,3-diethyloxirane-2-carbothioate (57)**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 8 Hz, $-CH_2CH_3$), 0.99 (t, 3H, J = 8 Hz, $-CH_2CH_3$), 1.52 (s, 9H, $-C(CH_3)_3$), 1.68 (q, 2H, J = 8 Hz, $-CH_2CH_3$), 1.70 (q, 2H, J = 8 Hz, $-CH_2CH_3$), and 3.42 (s, 1H, -CH-); ir 1695 and 1668 cm^{-1} (C=O); ms M^+ 216.1178 (calcd. for $C_{11}H_{20}O_2S$: 216.1184).

***S-tert*-Butyl 6-*tert*-butyl-1-oxaspiro[2.5]octane-2-carbothioates (58)**, ***trans*-58**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.87 (s, 9H, $-C(CH_3)_3$), 1.50 (s, 9H, $-SC(CH_3)_3$), 1.0-2.1 (complex, 9H), and 3.36 (s, 1H, -CHCO-). ***cis*-58**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.88 (s, 9H, $-C(CH_3)_3$), 1.40 (s, 9H, $-SC(CH_3)_3$), 1.0-2.1 (complex, 9H), and 3.38 (s, 1H, -CHCO-); ir 1695 and 1669 cm^{-1} (C=O); ms M^+ 284.1810 (calcd. for $C_{16}H_{28}O_2S$: 284.1809).

***S-tert*-Butyl 4-cyclohexyl-1-oxaspiro[2.5]octane-2-carbothioate (59)**: mp 91-93°C; ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.8-2.05 (complex, 20H), 1.49 (s, 9H, $-C(CH_3)_3$), and 3.23 (s, 1H, -CHCO-); ir 1653 cm^{-1} (C=O); ms M^+ 310.1969 (calcd. for $C_{18}H_{30}O_2S$: 310.1966). Anal. Calcd. for $C_{18}H_{30}O_2S$: C, 69.63; H, 9.74; S, 10.33. Found: C, 69.67; H, 9.96; S, 10.36.

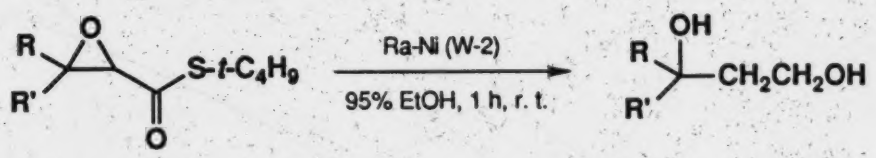
Reduction of glycidic thiolesters

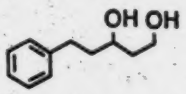
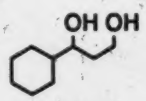
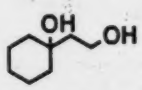
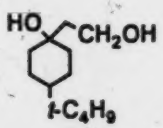
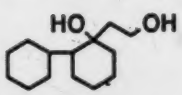
A. With Raney nickel

The reactions were carried out using the general procedure described below. Yields of products are shown in Table 6.

To Raney nickel (W-2, *ca.* 4 g / mmol of substrate, 50% slurry in water) in a flask, was added water (5 mL). After stirring for 0.5 min, the liquid was carefully removed with a pipet. The residue was washed three times with 95% ethanol (5 mL each). Then a solution of glycidic thiolester (0.5-1.0 mmol) in 5 mL of 95% ethanol was added. After stirring at room temperature for 1 h, the reaction mixture was filtered through a layer of celite 545. The residue was washed with 30 mL of ethanol. The filtrates were combined and concentrated to give a crude product which was subjected to either flash chromatography (3% methanol and 30% ethyl ether in hexane) giving a pure diol, or direct acetylation as follows.

Table 6. Reduction of Glycidic Thiolesters with Raney Nickel



Entry	Thiolester	Product	% Yield
1	*cis*-**53**	 **63**	80
2	**54** (isomeric mixture)	 **64**	88
3	**55**	 **65**	87
4	**58** (*cis*:*trans* 1:2)	 **66** (*cis*:*trrans* 1:2)	80
5	**59** (isomeric mixture)	 **67**	96

A pure or crude diol yielded from the reduction reaction was stirred with excess acetic anhydride and pyridine in methylene chloride at room temperature overnight. Then the mixture was poured into an ice-cold aqueous 1 *N* sodium hydroxide solution and extracted with methylene chloride. The extracts were washed with 1 *N* hydrochloric acid and

aqueous saturated sodium chloride solution, combined, dried, filtered and concentrated. The resulting residue was chromatographed (10-40% ethyl acetate in hexane) to give mono- and / or diacetate in good yield.

The diols and their corresponding mono- or diacetates were shown to have the following spectral data.

5-Phenyl-1,3-pentadiol (63): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.7-1.8 (complex, 4H), 2.3 (bs, 2H, D_2O exchangeable, -O**H**), 2.74 (ddd, 1H, *J* = 14, 7.5, 8.5 Hz, -C**H**HPh), 2.82 (ddd, 1H, *J* = 14, 7, 9 Hz, -CH**H**Ph), 3.8-4.0 (complex, 3H, -C**H**OHCH_2CH_2OH), and 7.2-7.4 (complex, 5H, Ar**H**); ir 3343 cm^{-1} (br, -OH); ms (CI) $(M + NH_4)^+$ 198.12 (calcd. for $C_{11}H_{20}NO_2$: 198.15). Diacetate of **63**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.8-2.0 (complex, 4H), 2.05 (s, 6H, -COCH_3), 2.64 (td, 2H, *J* = 7 , 2 Hz, -CH_2Ph), 4.10 (t, 2H, *J* = 6.5 Hz, -CH_2OAc), 5.04 (tt, 1H, *J* = 7, 5.5 Hz, -C**H**(OAc)-), and 7.15-7.40 (complex, 5H, Ar**H**); ir 1730 (C=O), 1500 and 1450 cm^{-1} (Ph); ms m/z 204.1148 (M^+ - CH_3CO_2H, calcd. for $C_{13}H_{16}O_2$: 204.1150).

1-Cyclohexyl-1,3-propanediol (64): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.9-1.5 (complex, 6H), 1.5-2.0 (complex, 7H), 2.30 (bs, 1H, D_2O exchangeable, -O**H**), 2.46 (bs, 1H, D_2O exchangeable, -O**H**), 3.68 (dt, 1H, *J* = 7.5, 5.5 Hz, -C**H**(OH)-), 3.90 (dt, 1H, *J* = 11, 5.5 Hz, -C**H**HOH), and 3.95 (dt, 1H, *J* = 11, 5 Hz, -CH**H**OH); ir 3342 (OH); ms (CI) $(M + NH_4)^+$ 176.20 (calcd. for $C_9H_{22}NO_2$: 176.17). Diacetate of **64**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.9-1.9 (complex, 13H,), 2.06 (s, 3H,

-$COCH_3$), 2.08 (s, 3H, -$COCH_3$), 4.12 (t, 2H, J = 7 Hz, -CH_2OAc), and 4.90 (ddd, 1H, J = 9, 6, 4 Hz, -CH(OAc)-).

1-(2-Hydroxyethyl)cyclohexanol (65): ^1H nmr (200 MHz, $CDCl_3$) δ 1.3-1.8 (complex, 10H), 1.76 (dd, 2H, J = 6, 5 Hz, -CH_2CH_2OH), 2.35 (bs, 1H, D_2O exchangeable, -OH), 2.80 (bs, 1H, D_2O exchangeable, -OH), and 3.90 (ddd, 2H, J = 6, 5, 4.5 Hz; after addition of D_2O, dd, 2H, J = 6; 5 Hz, -CH_2CH_2OH). Monoacetate of **65**: ^1H nmr (200 MHz, $CDCl_3$) δ 1.2-1.8 (complex, 11H), 1.82 (t, 2H, J = 8 Hz, -CH_2CH_2OAc), 2.06 (s, 3H, -$COCH_3$), and 4.27 (t, 2H, J = 8 Hz, -CH_2CH_2OAc); ir 3450 (OH), 1716 cm^{-1} (C=O); ms m/z 169.1227 (M^+ - OH, calcd. for $C_{10}H_{17}O_2$: 169.1228). Diacetate of **65**: ^1H nmr (200 MHz, $CDCl_3$) δ 1.2-1.6 (complex, 8H), 2.03 (s, 3H, -$COCH_3$), 2.06 (s, 3H, -$COCH_3$), 2.2 (complex, 2H), 2.25 (t, 2H, J = 8 Hz, -CH_2CH_2OAc), and 4.13 (t, 2H, J = 8 Hz, -CH_2CH_2OAc); ir 1725 cm^{-1} (C=O); ms m/z 169.1226 (M^+ - $OCOCH_3$, calcd. for $C_{10}H_{17}O_2$: 169.1228).

4-*tert*-Butyl-1-(2-hydroxyethyl)cyclohexanols (66): ir 3356 cm^{-1} (OH); ms M^+ 200.1776 (calcd. for $C_{12}H_{24}O_2$: 200.1776). *trans*-**66**: ^1H nmr (200 MHz, $CDCl_3$) δ 0.86 (s, 9H, -$C(CH_3)_3$), 1.2-2.2 (complex, 9H), 1.84 (t, H, J = 5.5 Hz, -CH_2CH_2OH), 2.68 (bs, 1H, -OH), 2.23 (bs, 1H, -OH), and 3.92 (t, 2H, J = 5.5 Hz, -CH_2OH). *cis*-**66**: ^1H nmr (200 MHz, $CDCl_3$) δ 0.88 (s, 9H, -$C(CH_3)_3$), 1.2-2.2 (complex, 9H), 1.73 (t, 2H, J = 5.5 Hz, -CH_2CH_2OH), 2.68 (bs, 1H, -OH), 2.23 (bs, 1H, -OH), and 3.95 (t, 2H, J = 5.5 Hz, -CH_2CH_2OH). Monoacetate of *trans*-**66**: ^1H nmr (200 MHz, $CDCl_3$) δ 0.86 (s, 9H, -$C(CH_3)_3$), 1.0-2.0 (complex, 10H),

1.88 (t, 2H, J = 7 Hz, -CH_2CH_2OAc), 2.06 (s, 3H, -$COCH_3$), and 4.26 (t, 2H, J = 7 Hz, -CH_2OAc). Monoacetate of *cis*-**66**: ^1H nmr (200 MHz, $CDCl_3$) δ 0.86 (s, 9H, -$C(CH_3)_3$), 1.2-1.8 (complex, 10H), 1.78 (t, 2H, J = 7 Hz, -CH_2CH_2OAc), 2.05 (s, 3H, -$COCH_3$), and 4.27 (t, 2H, J = 7 Hz, -CH_2OAc).

2-Cyclohexyl-1-(2-hydroxyethyl)cyclohexanol (67): mp 104-107°C; ^1H nmr (200 MHz, $CDCl_3$) δ 1.0-2.1 (complex, 22H), 2.28 (ddd, 1H, J = 14, 10, 6 Hz, -CHHCH_2OH), 2.46 (bs, 1H, D_2O exchangeable, -OH), 3.80 (ddd, 1H, J = 10, 6, 4.5 Hz, -CHHOH), and 4.01 (ddd, 1H, J = 10, 10, 4 Hz, -CHHOH); ir 3362 (OH), 3357 cm^{-1} (OH); ms M^+ 226.1929 (calcd. for $C_{14}H_{26}O_2$: 226.1933). Monoacetate of **67**: ^1H nmr (200 MHz, $CDCl_3$) δ 1.0-1.9 (complex, 21H), 1.97 (t, 2H, J = 7 Hz, -CH_2CH_2OAc), 2.10 (s, 3H, -$COCH_3$), and 4.23 (t, 2H, J = 7 Hz, -CH_2OAc).

B. With sodium borohydride

The reactions were carried out using the general procedure described below. Yields of products are shown in Table 7.

To a solution of a glycidic thiolester (0.5-1.0 mmol) in 98% ethanol (1-2 mL) cooled by an ice bath, was added sodium borohydride (4.0 molar equivalents) with stirring. After 10 min, the ice bath was removed and the reaction mixture was stirred at room temperature for 4-8 h. After the glycidic thiolester was completly consumed as shown by thin layer

chromatography, 1 *N* hydrochloric acid (5 mL) was carefully added to the mixture. The resulting mixture was poured into 1 *N* aqueous sodium hydroxide solution (50 mL) and extracted with methylene chloride (3 x 15 mL). The extracts were washed with aqueous saturated sodium chloride solution, combined, dried, filtered and concentrated. The residue was chromatographed (30-60% ethyl acetate in hexane) to afford the epoxy alcohol.

C. With lithium aluminum hydride at -78°C

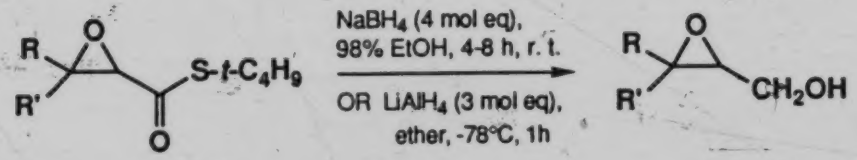
The reactions were carried out using the general procedure described below. Yields of products are shown in Table 7.

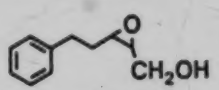
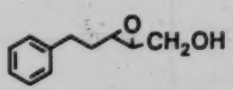
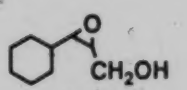
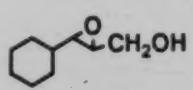
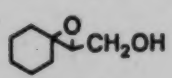
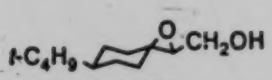
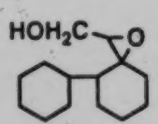
At -78°C, to a solution of a glycidic thiolester (0.5-1.0 mmol) in ethyl ether (3-6 mL) under an atmosphere of argon, was carefully added lithium aluminum hydride (3.0 molar equivalents). The reaction mixture was stirred at -78°C for 1 h, then quenched by addition of water (1 mL). The resulting mixture was acidified with 1 *N* hydrochloric acid and extracted with methylene chloride (3 x 10 mL). The extracts were washed with aqueous saturated sodium chloride solution, combined, dried, filtered and concentrated. The residue was chromatographed (30-60% ethyl acetate in hexane) to give the corresponding epoxy alcohol.

The epoxy alcohols obtained from the sodium borohydride and lithium aluminum hydride reductions of glycidic thiolesters showed the following spectral data.

Table 7. Reduction of Glycidic Thiolesters

with Sodium Borohydride and Lithium Aluminum Hydride



Thiolester	Product	% Yield with $NaBH_4$	% Yield with $LiAlH_4$
cis-53	 *cis*-69	94	94
trans-53	 *trans*-69	80	
cis-54	 *cis*-70	90	83
trans-54	 *trans*-70		89
55	 68	82	
cis-58	 *cis*-71		92
59 (isomeric mixture)	 72 (isomeric mixture)	95	86

2-Hydroxymethyl-3-(2-phenylethyl)oxiranes (69), *cis*-**69**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.57 (bs, 1H, D_2O exchangeable, -O**H**), 1.81 (dddd, 1H, *J* = 14, 8.5, 8, 6 Hz, -CH_2C**H**H-), 1.95 (dddd, 1H, *J* = 14, 9, 8, 6.5 Hz, -CH_2CH**H**-), 2.78 (dt, 1H, *J* = 13, 8 Hz, PhC**H**H-), 2.91 (ddd, 1H, *J* = 13, 9, 6. Hz, PhCH**H**-), 3.12 (ddd, 1H, *J* = 8.5, 6.5, 4 Hz, -CH_2C**H**-), 3.15 (dt, 1H, *J* = 4, 5 Hz, -C**H**CH_2OH), 3.62 (d, 2H, *J* = 5 Hz, -C**H**$_2$OH), and 7.25-7.45 (complex, 5H, Ar**H**); ir 3417 and 3409 (OH); ms $M^{+\cdot}$ 178.0988 (calcd. for $C_{11}H_{14}O_2$: 178.0994). Acetate of *cis*-**69**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.94 (dt, 2H, *J* = 6, 8 Hz, -CH_2C**H**$_2$-), 2.12 (s, 3H, -COC**H**$_3$), 2.80 (dt, 1H, *J* = 14, 8 Hz, PhC**H**H-), 2.84 (dt, 1H, *J* = 14, 8 Hz, PhCH**H**-), 2.95 (ddd and dt, 2H, *J* = 6, 6, 3 and 6, 6 Hz, -CH_2C**H**OC**H**CH_2OH), 3.90 (dd, 1H, *J* = 12, 6 Hz, -C**H**HOH), 4.34 (dd, 1H, *J* = 12, 3 Hz, -CH**H**OH), and 7.25-7.45 (complex, 5H, Ar**H**). *trans*-**69**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.58 (bs, 1H, D_2O exchangeable, -O**H**), 1.90 (ddd, 1H, *J* = 8.5, 8, 6 Hz, -CH_2C**H**H-), 1.94 (ddd, 1H, *J* = 8, 6.5, 6 Hz, -CH_2CH**H**-), 2.80 (ddd, 1H, *J* = 14, 8, 8 Hz, PhC**H**H-), 2.85 (ddd, 1H, *J* = 14, 8.5, 6.5 Hz, PhCH**H**-), 2.88 (ddd, 1H, *J* = 4.5, 2.5, 2 Hz, -CH_2C**H**-), 3.03 (dt, 1H, *J* = 2, 6 Hz, -C**H**CH_2OH), 3.62 (dd, 1H, *J* = 12, 4.5 Hz, -C**H**HOH), 3.88 (dd, 1H, *J* = 12.5, 2.5 Hz, -CH**H**OH), and 7.25-7.45 (complex, 5H, Ar**H**); ir 3417 and 3409 cm^{-1} (OH).

2-Hydroxymethyl-3-cyclohexyloxiranes (70), *cis*-**70**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.0-1.9 (complex, 11H), 2.02 (bs, 1H, -O**H**), 2.80 (dd, 1H, *J* = 8, 4 Hz, -CHC**H**-), 3.22 (ddd, 1H, *J* = 7, 4, 4 Hz, -C**H**CH_2-), 3.76 (dd, 1H, *J* = 12, 7 Hz, -C**H**HOH), and 3.93 (dd, 1H, *J* = 12, 4 Hz,

-CHHOH); ir 3418 cm^{-1} (OH). *trans*-**70**: ^1H nmr (200 MHz, $CDCl_3$) δ 1.0-2.0 (complex, 12H), 2.80 (dd, 1H, J = 7, 2.5 Hz, -CHCH-), 3.03 (ddd, 1H, J = 4, 2.5, 2.5 Hz, -$CHCH_2$-), 3.67 (ddd, 1H, J = 12, 7, 4 Hz, -CHHOH), and 3.95 (ddd, 1H, J = 12, 8, 2.5 Hz, -CHHOH); ir 3418 cm^{-1} (OH); ms (CI) $(M + NH_4)^+$ 174.11 (calcd. for $C_9H_{20}NO_2$: 174.15).

2-Hydroxymethyl-1-oxaspiro[2.5]octane (**68**): ^1H nmr (200 MHz, $CDCl_3$) δ 1.4-1.9 (complex, 11H), 3.00 (dd, 1H, J = 7, 4.5 Hz, -$CHCH_2OH$), 3.70 (ddd, 1H, J = 12, 7, 4.5 Hz, -CHHOH), and 3.81 (ddd, 1H, J = 12, 8, 4.5 Hz, -CHHOH); ir 3400 cm^{-1} (OH); ms (CI) $(M + NH_4)^+$ 160 (calcd. for $C_8H_{18}NO_2$; 160); Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.57; H, 10.11.

***cis*-6-*tert*-Butyl-2-hydroxymethyl-1-oxaspiro[2.5]octane** (*cis*-**71**): ^1H nmr (200 MHz, $CDCl_3$) δ 0.90 (s, 9H, -$C(CH_3)_3$), 1.0-2.0 (complex, 10H), 3.05 (dd, 1H, J = 7, 4.5 Hz, -$CHCH_2OH$), 3.76 (ddd, 1H, J = 12, 7, 4 Hz, -CHHOH), and 3.87 (ddd, 1H, J = 12, 7, 4.5 Hz, -CHHOH); ir 3400 cm^{-1} (OH); ms M^+ 198.1629 (calcd. for $C_{12}H_{22}O_2$: 198.1620).

4-Cyclohexyl-2-hydroxymethyl-1-oxaspiro[2.5]octane (**72**): ^1H nmr (200 MHz, $CDCl_3$) δ 0.9-2.1 (complex, 21H), 2.85 (dd, 1H, J = 5, 7 Hz, -$CHCH_2OH$), 3.70 (ddd, 1H, J = 12, 7, 5 Hz, -CHHOH), and 3.90 (ddd, 1H, J = 12, 5, 7.5 Hz, -CHHOH); ir 3420 cm^{-1} (OH); ms M^+ 224.1778 (calcd. for $C_{14}H_{24}O_2$: 224.1776); Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.82; H, 10.45.

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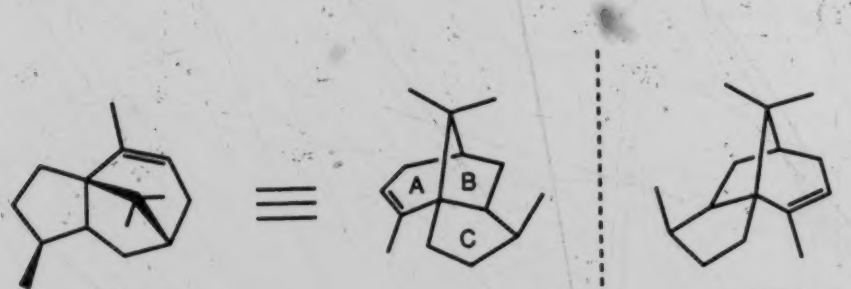
CHAPTER II

STUDIES ON THE TOTAL SYNTHESIS OF α-PATCHOULENE

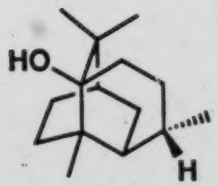
INTRODUCTION

α-Patchoulene (**74**) is a tricyclic sesquiterpene which was isolated[1] from *Naraostadus jatamansi* and patchouli oil. The commercially available patchouli oil is obtained from the leaves of *Pogostemon cablin*,[2, 3] and is an important material in the perfume industry.



(+)-**74** (-)-**74**

The structure of α-patchoulene was identified by Büchi and coworkers in early 1960's.[2] During their studies on the structure of patchouli alcohol (**75**), it was found that dehydration[4] of patchouli alcohol (**75**) with phosphorus oxychloride in pyridine or *via* pyrolysis of the corresponding acetate (**76**) produced a mixture of α- (**74**), β- (**77**) and γ-patchoulene (**78**). It was recognized[5, 6] later that the dehydration proceeded with a concomitant Wagner-Meerwein rearrangement reaction. Thus, α-patchoulene possesses a tricyclo[5.3.1.$0^{1,5}$]undecane ring system, which is also the parent skeleton of several closely related sesquiterpenes such as α-patchoulenone (**79**),[7] sugeonol (**80**),[8] cyperene (**81**),[9] and cyperotundone (**82**)[10] isolated from *Cyperus rotundus* L. tuber oil. The



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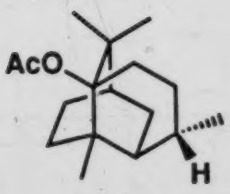

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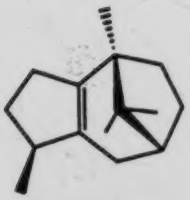

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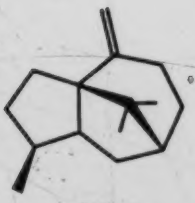

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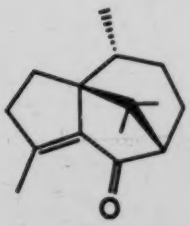

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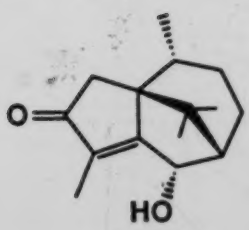

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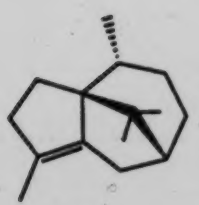

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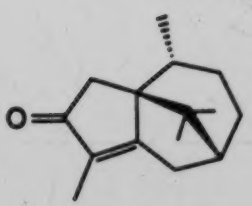


82

structural assignment of α-patchoulene was confirmed by a total synthesis.[5]

In this synthesis, (-)-homocamphor (**83**) was used as starting material. By a short synthetic sequence as outlined in Scheme 15, the key intermediate β-patchoulene oxide (**84**) was prepared. Acid catalyzed rearrangement of this compound followed by hydroboration with oxidative workup gave diol **85**. Subsequent modification of diol **85** gave α-patchoulene (**74**). The same type of acid catalyzed rearrangement reaction was also used as a key step in the partial synthesis of α-patchoulenone (**79**), cyperene (**81**) and cyperotundone (**82**) reported by Hikino and coworkers in 1968.[9]

In another synthesis of α-patchoulenone (**79**),[11] the bicyclic A/B ring skeleton **86** was achieved by an intramolecular addition of diazoketone to olefin. As summarized in Scheme 16, subsequent modification of compound **86**, including a three-carbon chain extension and an annulation of ring C by intramolecular aldol condensation, gave the natural ketone in racemic form.

In 1977, an interesting synthetic approach to α-patchoulene (**74**) was devised by Deslongchamps and coworkers.[12] They recognized that a tetracyclic compound such as **87** could serve as a common intermediate for synthesis of both α-patchoulene (**74**) and α-cydrene (**88**) by selective cleavage of the cyclopropane ring. Selective cleavage of bond **a** (path A) was expected to lead eventually to the formation of α-patchoulene

(74). On the other hand, path B involving bond **b** cleavage could give the tricyclic skeleton of α-cedrene. Experimentally, intermediate **87** was successfully prepared in a route as described in Scheme 17. The selective cleavage of bond **a** and bond **b** in compound **87** was carried out under thermodynamically and kinetically controlled conditions respectively. However, further elaboration on compounds **89** and **90** to the target molecules remains to be accomplished.

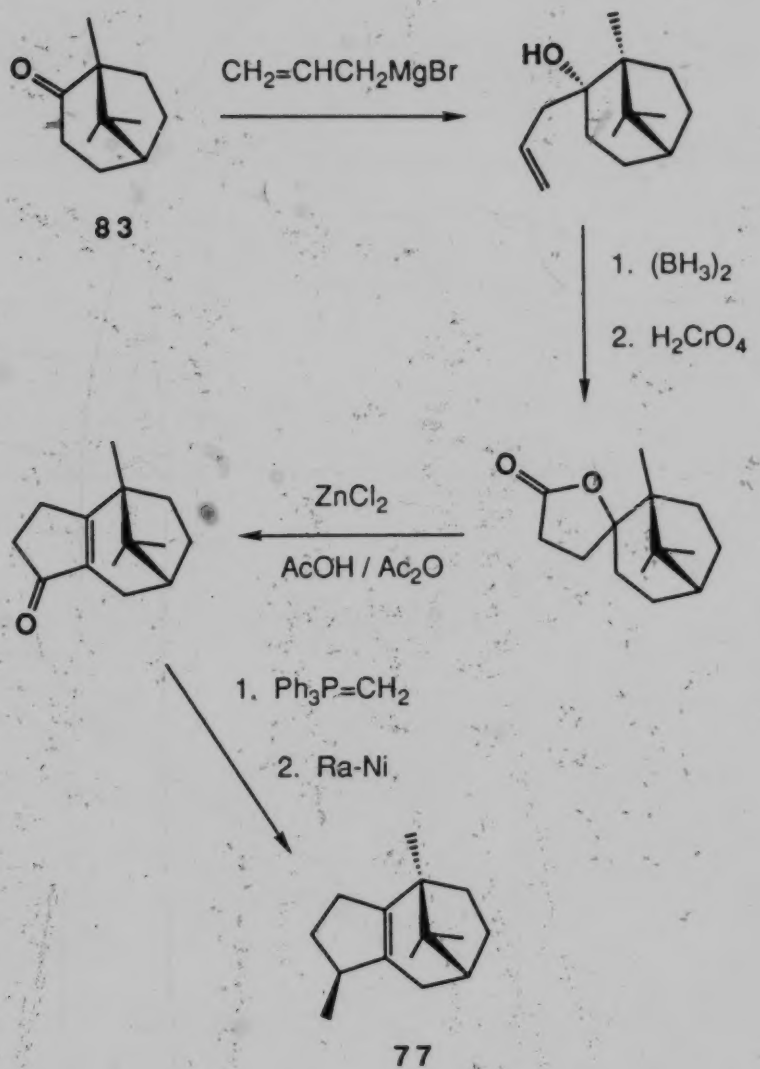
Several years ago, a study on the total synthesis of α-patchoulene from *l*-(-)-10-camphorsulfonic acid (**91**) was initiated in this laboratory. In the original synthetic plan,[13] trione **92** was conceived as a key intermediate. This compound was expected to undergo intramolecular Michael addition (**92**→**93**) and aldol reaction (**93**→**94**) to give the desired tricyclic framework of the target molecule (Scheme 18). Considerable efforts were devoted to the preparation of this projected key intermediate, however, without much success. During the course of these studies, a new approach emerged. In this approach, the construction of the bicyclo[3.2.1]octane system present in the target molecule was effected by the rearrangement of keto epoxide **109** to diketo alcohol **95**. To complete the synthesis from **95**, it remains to form the C ring of the target molecule **74**.

This five-membered ring could, in principle, be accomplished in three ways as outlined in Schemes 19, 20 and 21. The key step in Route 1 (Scheme 19) is an intramolecular coupling reaction whereby diketone **96** is expected to cyclize to the required tricyclic intermediate. A number

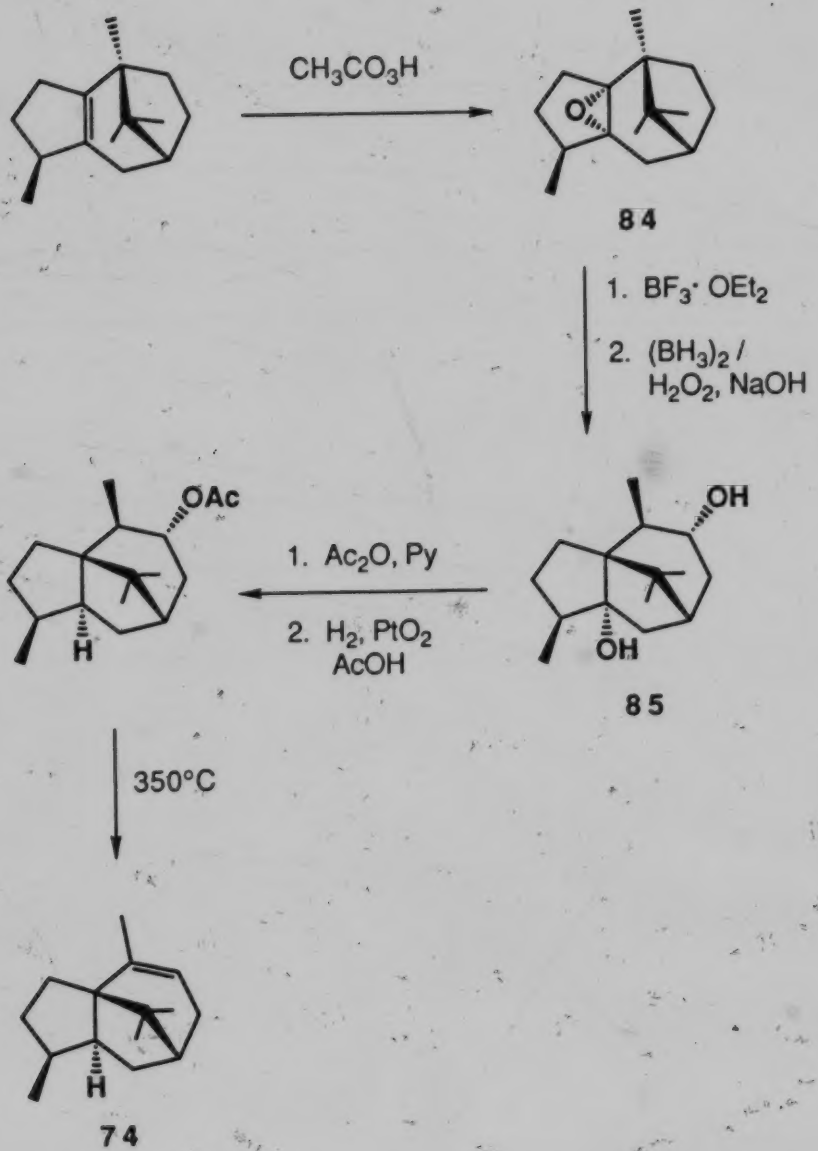
of examples of this type of transformation have been successfully carried out using active titanium metal by the method developed by McMurry and others.[14] The required precursor **96** for this key operation could be obtained from aldehyde **97** by a three-carbon extension of the aldehyde group involving a Horner-Emmons reaction.

In each of Route 2 (Scheme 20) and Route 3 (Scheme 21), an intramolecular aldol condensation is used to induce cyclization. The fundamental difference of these two synthetic routes lies in the means by which required carbon units and functional groups are incorporated. Route 2 makes use of the cyclopentanone carbonyl as the starting point for the incorporation of the acetyl group (as shown in structural formula **98**) which is required for the aldol process. In Route 3 the hydroxy methyl group in compound **95** will be converted to the aldehyde group as shown in the compound **99** . Addition of 1-nitropropane[15] followed by functional group modifications including a Nef reaction[16] could lead to diketone **100**. Its aldol condensation is expected to provided the tricyclic framework of α-patchoulene.

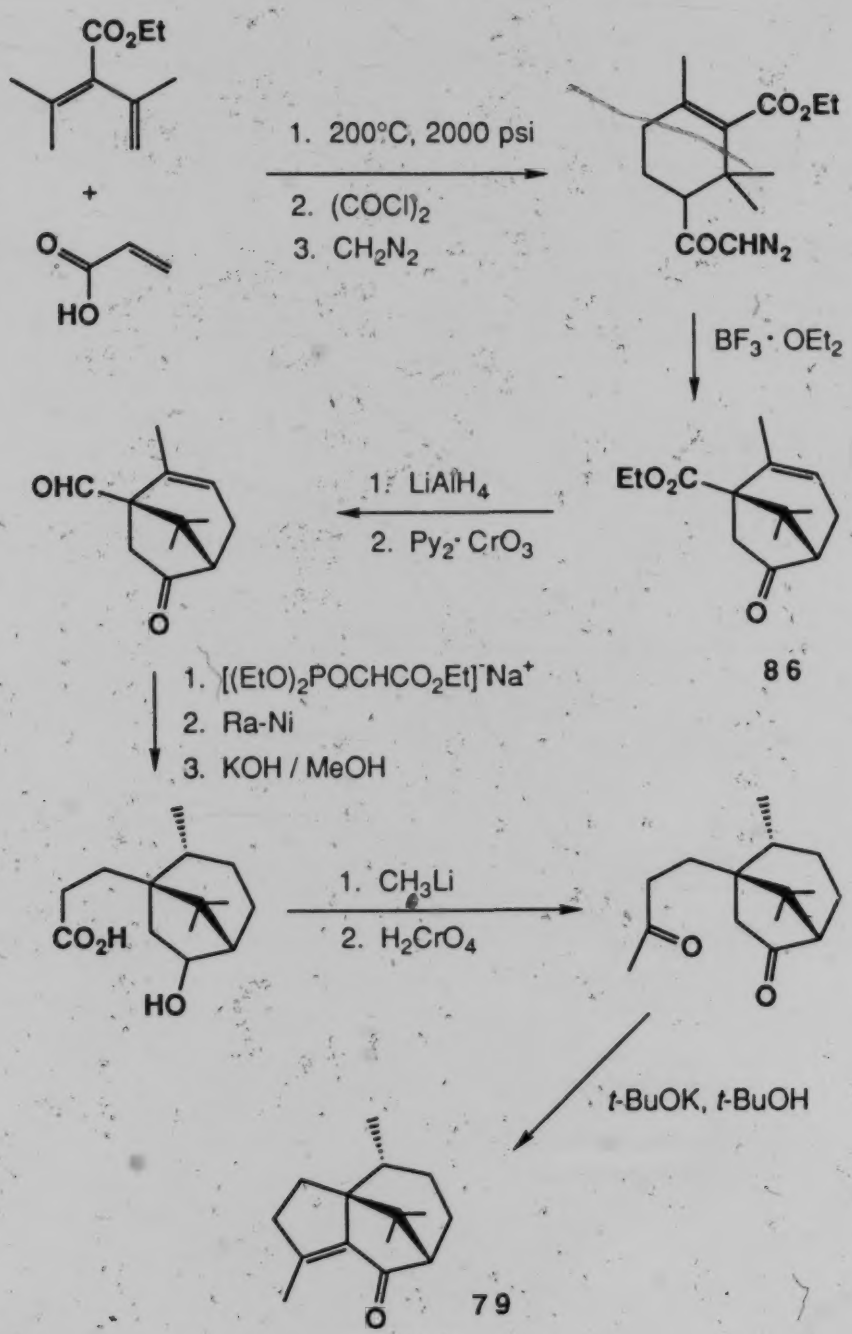
The above routes were examined in our studies directed towards the total synthesis of α-patchoulene. The results are discussed in Chapter II of this thesis.


O
CH2=CHCH2MgBr
HO
83
1. (BH3)2
2. H2CrO4
O
O
ZnCl2
AcOH / Ac2O
O
1. Ph3P=CH2
2. Ra-Ni
77

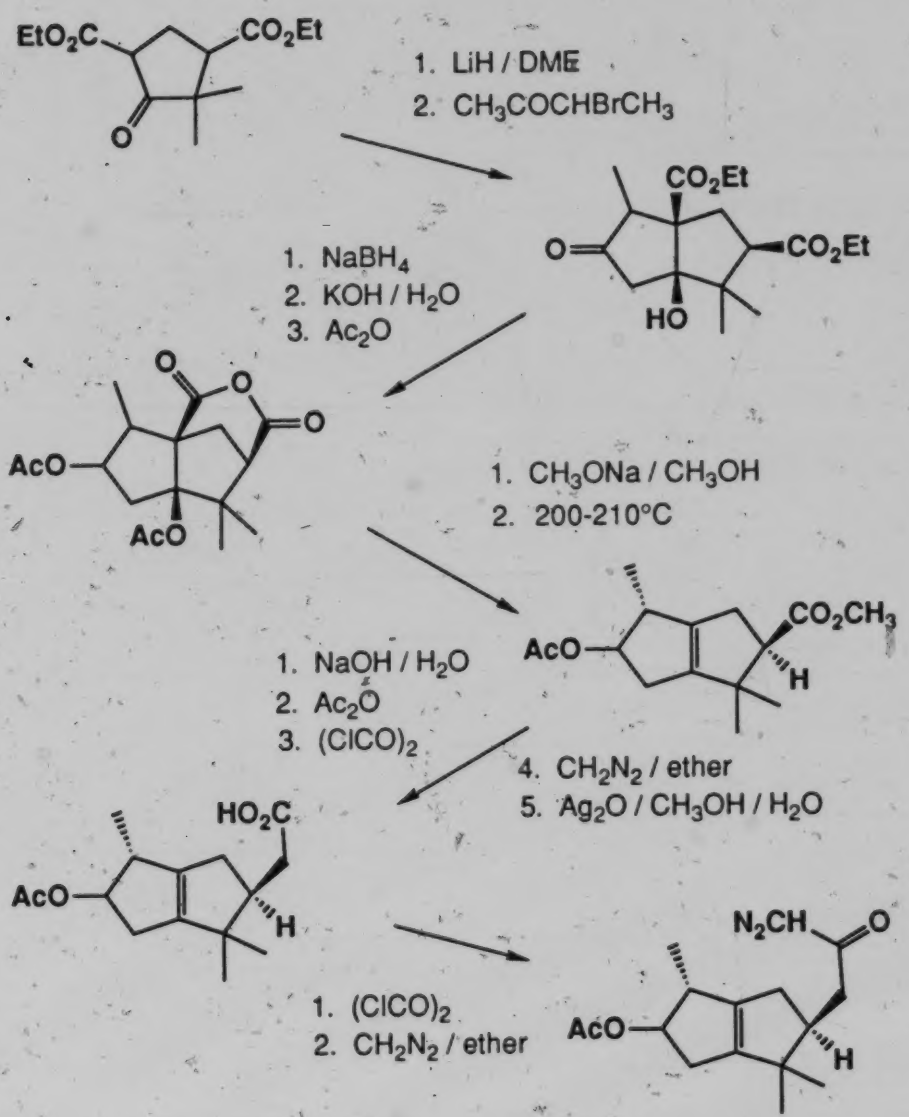
Scheme 15.



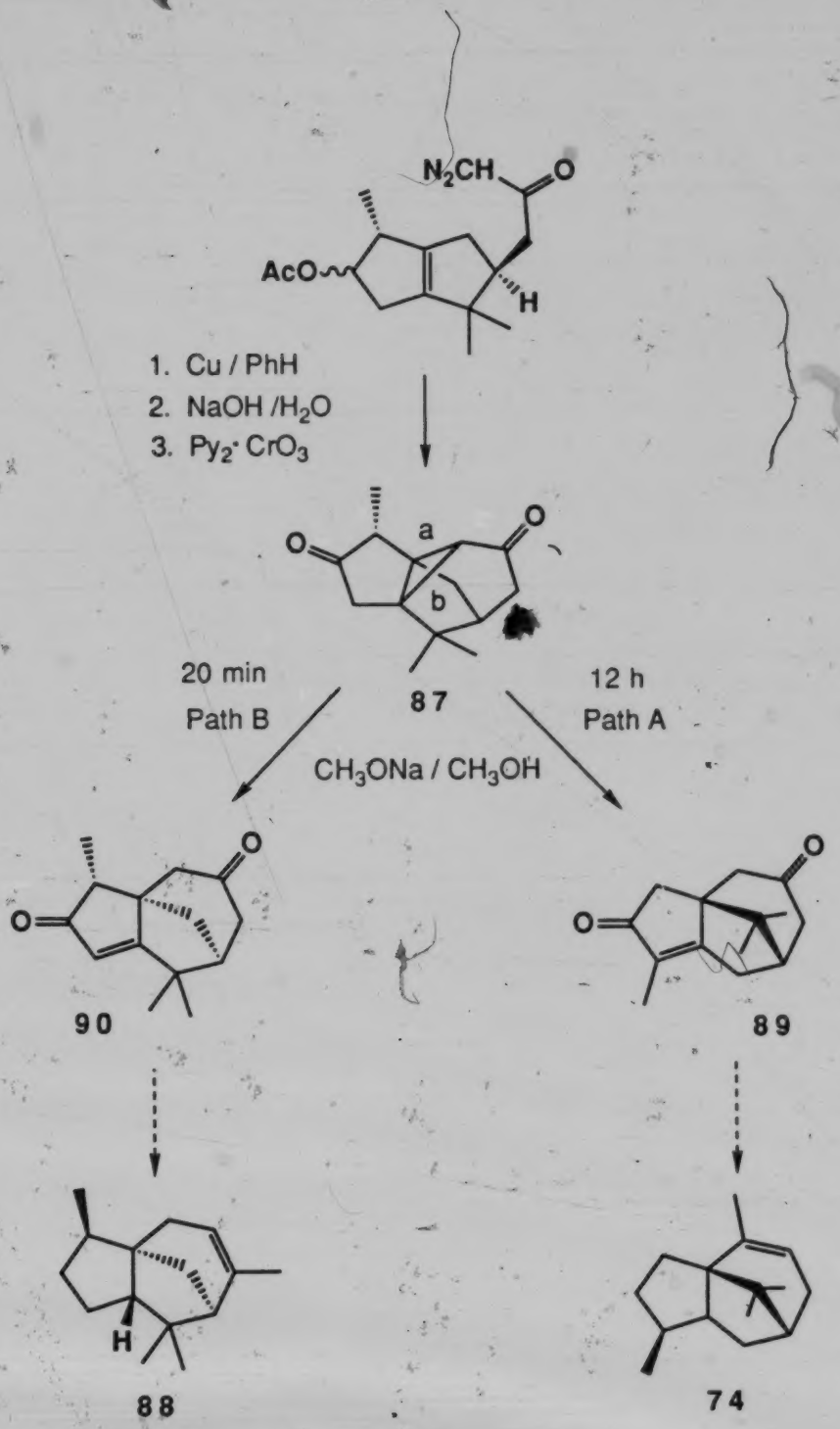
Scheme 15. (continued)


CO2Et
+
O
HO
1. 200°C, 2000 psi
2. (COCl)2
3. CH2N2
CO2Et
COCHN2
BF3· OEt2
EtO2C
O
86
1. LiAlH4
2. Py2· CrO3
OHC
O
1. [(EtO)2POCHCO2Et]⁻Na⁺
2. Ra-Ni
3. KOH / MeOH
CO2H
HO
1. CH3Li
2. H2CrO4
O
O
t-BuOK, t-BuOH
O
79

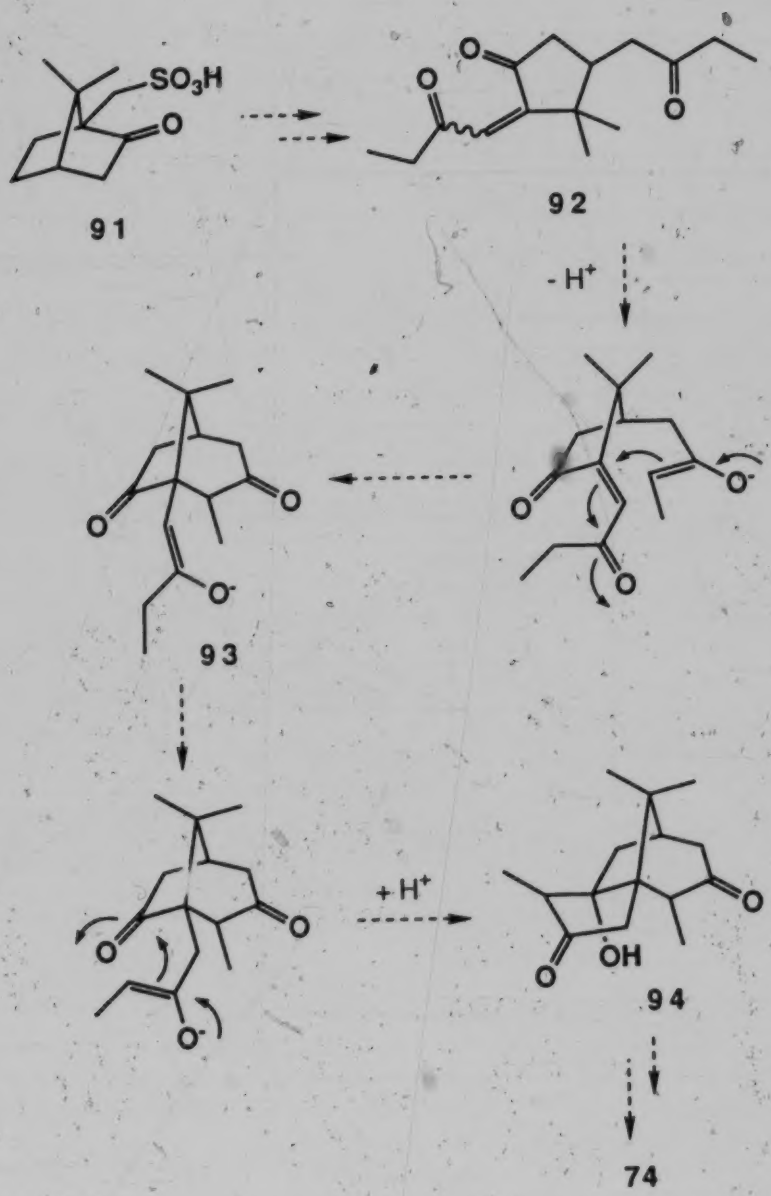
Scheme 16.


EtO2C
CO2Et
O
1. LiH / DME
2. CH3COCHBrCH3
CO2Et
O
CO2Et
HO
1. NaBH4
2. KOH / H2O
3. Ac2O
O
O
O
AcO
AcO
1. CH3ONa / CH3OH
2. 200-210°C
CO2CH3
AcO
H
1. NaOH / H2O
2. Ac2O
3. (ClCO)2
4. CH2N2 / ether
5. Ag2O / CH3OH / H2O
HO2C
AcO
H
N2CH
O
AcO
H
1. (ClCO)2
2. CH2N2 / ether

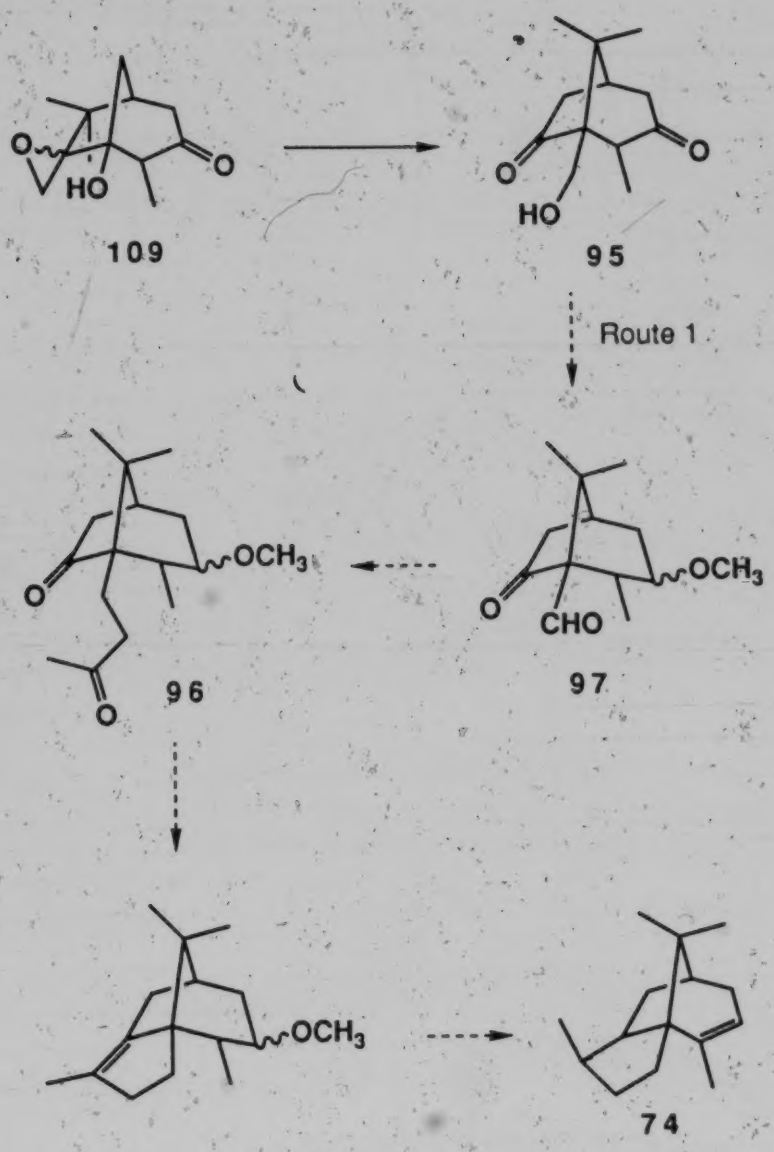
Scheme 17.



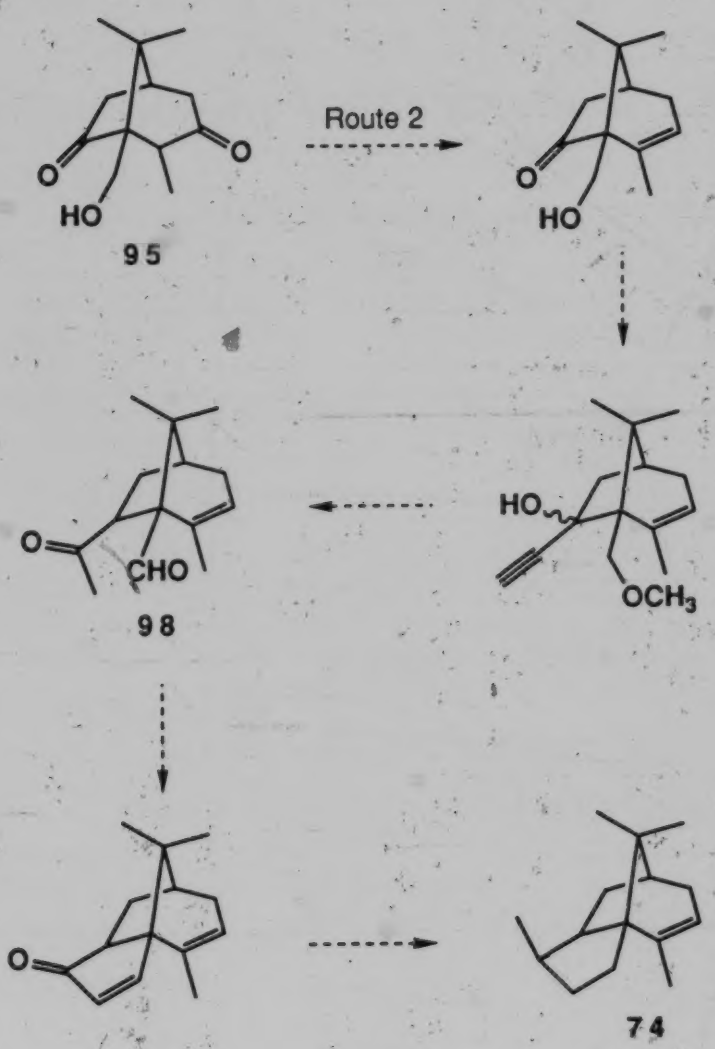
Scheme 17. (continued)



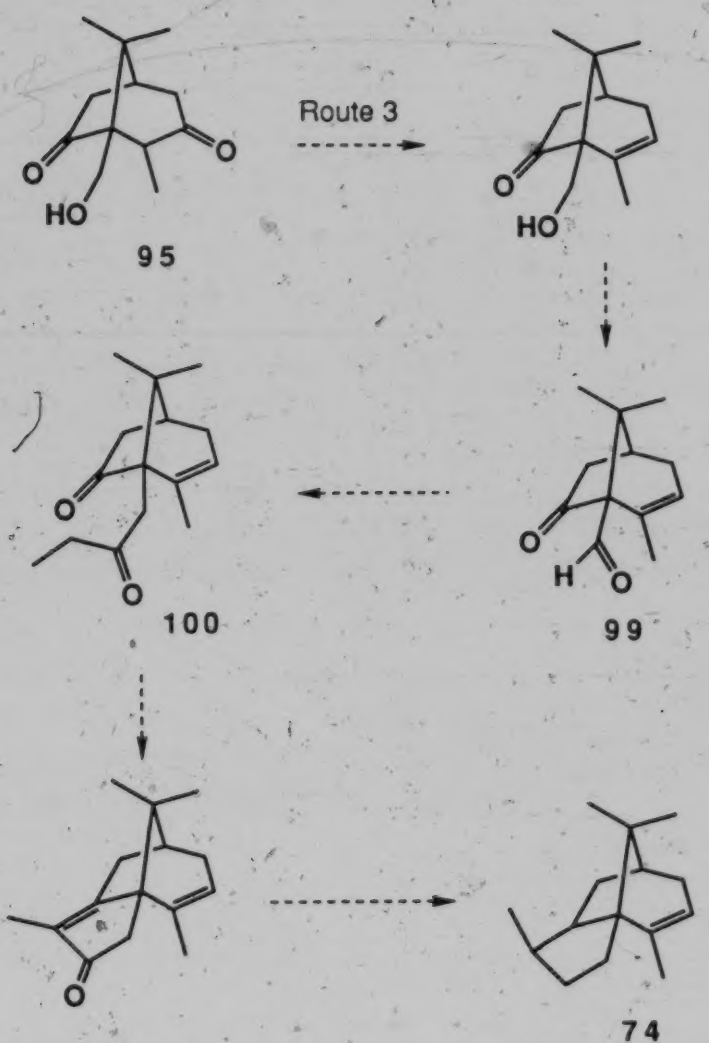
Scheme 18



Scheme 19



Scheme 20.

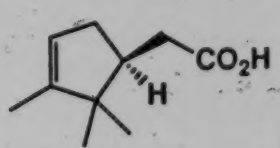


Scheme 21

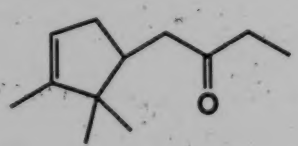
RESULTS AND DISCUSSION

1. Construction of bicyclo[3.2.1]octane framework

As discussed previously, the tricyclic carbon framework of α-patchoulene could, in principle, be constructed from compound **95** by either the aldol or the McMurry approach. The preparation of key intermediate **95** was carried out following a route developed earlier in this laboratory.[13] It has been shown that fusion of *l*-10-camphorsulfonic acid salt with potassium hydroxide gave (-)-campholenic acid [(-)-**101**] which possesses the same chirality as that of α-patchoulene at C-1. For the present work, the less expensive *dl*-10-camphorsulfonic acid sodium salt was used as starting material. Thus, all the synthetic products described herein were obtained as racemic mixtures.



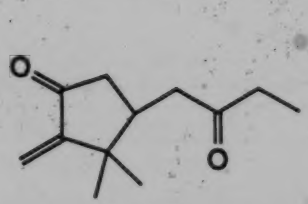
(-)-**101**



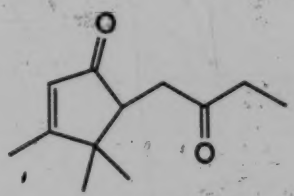
102

dl-10-Camphorsulfonic acid sodium salt was heated with a mixture of potassium hydroxide and sodium hydroxide to give a 76% yield of campholenic acid **101** in racemic form. This carboxylic acid was treated sequentially with lithium hydride and ethyllithium, and the corresponding ethyl ketone **102** was obtained in 91% yield.

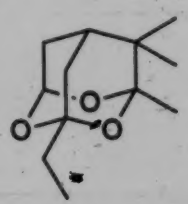
Enone **102** was subjected to photo-oxygenation in methylene chloride in the presence of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP), acetic anhydride, pyridine and 4-(dimethylamino)pyridine (DMAP). The reaction gave rise to diketone **103** in 55% yield, along with several by-products, two of which were identified as compounds **104** and **105**.



103



104



105

The ir spectrum of compound **103** showed absorption bands at 1724 cm^{-1} for the carbonyl groups and at 1633 cm^{-1} for the double bond. A molecular ion peak at 194.1305 in the mass spectrum was consistent with the required molecular formula of $C_{12}H_{18}O_2$. In the ^1H nmr spectrum, two one-proton signals at δ 5.98 and 5.22 were observed for the vinylic protons, along with three methyl signals, a triplet (J = 7.5 Hz) at δ 1.07 and two singlets at δ 1.02 and 1.24.

The ir spectrum of compound **104** also displayed absorption bands at 1701 and 1619 cm^{-1} for the carbonyl groups and the double bond respectively. The molecular ion peak in the mass spectrum indicated the same molecular formula as compound **103**. In the ^1H nmr spectrum, a one-proton signal at δ 5.84 was shown for the vinylic hydrogen, along

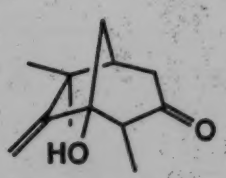
with four methyl signals, three singlets at δ 0.96, 1.27, 2.03 and a triplet at δ 1.09.

Compound **105** showed no absorption bands for either carbonyl or hydroxy group in the ir spectrum. Its molecular formula of $C_{12}H_{20}O_3$ was indicated by the molecular ion peak at 212.1413 in the mass spectrum. In the ^1H nmr spectrum, three methyl singlets appeared at δ 1.11, 1.15 and 1.25. A triplet at δ 0.93 and a quartet at δ 1.59 with the same coupling constant of 7.5 Hz were due to the ethyl group. A doublet of doublets at δ 5.26 (J = 2.5, 2 Hz) was assigned to the acetal hydrogen, which was found to couple with signals at δ 1.86 and 2.27. These two signals , which were mutually coupled to each other (12 Hz), were due to the adjacent methylene group. Signals for the other methylene group were found at δ 1.80 and 2.17. The last signal, a multiplet at δ 1.85, could be readily assigned to the remaining methine proton.

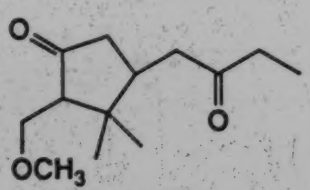
The aldol cyclization of diketone **103** was carried out in methanol at room temperature using potassium carbonate as a base. Under these conditions, the desired product **106** was obtained as a single stereoisomer in 49% yield (64 % based on consumed starting material) along with a 26% yield of the addition product **107** and a 24% recovery of the starting material. The ir spectrum of enone alcohol **106** showed a hydroxy absorption at 3445 cm^{-1}, a carbonyl absorption at 1702 cm^{-1} and a double bond absorption at 1655 cm^{-1}. In the mass spectrum, a molecular ion peak at 194.13405 indicated that this compound was isomeric with the starting diketone **103**. In the ^1H nmr spectrum, two one-

proton singlets at δ 5.07 and 5.04 were observed for the vinylic protons, along with three methyl signals, a doublet (J = 7.5 Hz) at δ 1.10 and two singlets at δ 1.00 and 1.20. Although compound **106** was obtained as a single stereoisomer, its stereochemistry at the chiral center bearing the methyl group could not be assigned unambiguously.

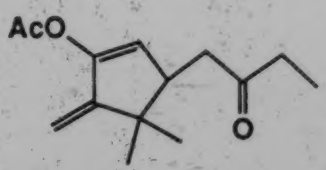
The structure of by-product **107** also followed clearly from its spectral data. The ir spectrum showed two carbonyl absorption bands at 1739 and 1714 cm^{-1}. The molecular formula of $C_{13}H_{22}O_3$ was indicated by the molecular ion peak at 226.1570 in the mass spectrum. In the ^1H nmr spectrum, a singlet at δ 3.34 and two doublets of doublets at δ 3.42 and 3.66 were observed for the ether group, along with a triplet at δ 1.07 and a quartet at δ 2.48 with the same coupling constant of 7.5 Hz for the ethyl group. Signals for the geminal methyl groups were shown at δ 0.75 and 1.21.



106



107



108

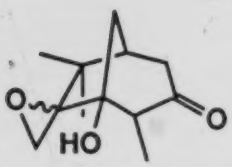
In order to improve the conversion of diketone **103** to compound **106** *via* the reversible aldol reaction, the following trapping method was attempted. Diketone **103** was treated with DMAP, pyridine and acetic anhydride in methylene chloride at room temperature as well as under

reflux. Unfortunately, no cyclization product was formed. The only product obtained was enol acetate **108** which showed, in the ^1H nmr spectrum, three one-proton singlets at δ 4.85, 4.75 and 4.65 for the vinylic protons, and four methyl signals, a triplet at δ 1.00 and three singlets at δ 0.95, 1.15 and 2.15. The molecular formula of $C_{14}H_{20}O_3$ was indicated by the molecular ion peak at 236.1414 in the mass spectrum.

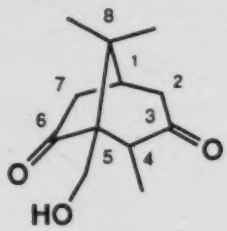
In principle, upon treatment with potassium carbonate in methanol, ether **107** could eliminate methanol to give diketone **103** and could be eventually converted to the desired compound **106**. In practice, however, treatment of **107** with potassium carbonate in methanol at room temperature gave rise to a complex mixture from which compound **106** could not be isolated.

Enone alcohol **106** was subjected to epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) in methylene chloride at room temperature for 6 h. The purification of the crude material by chromatography on silica gel afforded a mixture of two epimeric epoxides **109** (85% yield), which were found to be in the ratio of 1:3 according to the ^1H nmr spectrum, and diketo alcohol **95** (10% yield). The epimeric mixture could be partially separated by repeating the flash chromatography for the second time. The slower moving minor epimer was assigned the *endo* stereochemistry based on the observation that it was less prone to the subsequent rearrangement reaction to give **95**. Treatment of the epimeric mixture of **109** with stannic chloride in chloroform at 0-20°C for

2 h afforded 85% yield of **95** with about 10% recovery of the minor epimer in pure form. After a longer period of reaction time (10 h), however, both epimers were completely consumed resulting in a 90% yield of compound **95**. These experimental results indicated that the rate of rearrangement of the minor epimer was slower than the major epimer.



109



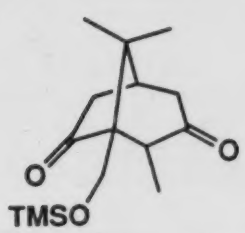
95

The structure of compound **95** was confirmed by its spectral data. In the ir spectrum, a hydroxy absorption band at 3485 cm^{-1} and two carbonyl absorptions at 1733 and 1704 cm^{-1} characteristic of five-membered and six-membered ring ketone, respectively. A molecular ion peak at 210.1257 in the mass spectrum was consistent with the required molecular formula of $C_{12}H_{18}O_3$. The ^1H nmr spectrum displayed two methyl singlets at δ 1.16 and 1.42 as well as a methyl doublet (J = 7.0 Hz) at δ 1.09. The latter signal was found to be mutually coupled with the quartet at δ 3.03, which was attributed to the proton at C-4. The presence of the hydroxymethyl unit was evident from the doublets at δ 3.92 and 3.75, which were shown to couple with each other with a large geminal coupling constant of 12 Hz, and the singlet at δ 1.65 which disappeared upon addition of deuterium oxide. Also in agreement with the assigned structure were signals at δ 2.22, a doublet of doublets of

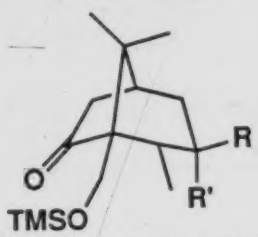
doublets with coupling constants of 7, 4 and 3 Hz due to the proton at C-1, δ 2.60 and 1.98 for the methylene protons at C-7, the former as a doublet of doublets of doublets (J = 19, 7 and 2 Hz) and the latter as a doublet with a large geminal coupling constant of 19 Hz. The methylene protons of the six-membered ring ketone appeared at δ 2.39 and 2.90 coupled to each other with a large coupling constant of 17 Hz. The proton in the lower field (δ 2.90) was further coupled to the proton at C-1 (J = 4 Hz) and the proton at C-7 (J = 2 Hz), while only one additional coupling was observed for the proton in the higher field (J = 3 Hz). The stereochemistry of **95** at C-4 could not be deduced from the available spectral data. Its assignment follows from the subsequent transformations.

Hydroxy diketone **95** possesses the A and B rings of α-patchoulene. The conversion of this intermediate to the target molecule requires a five-membered ring annulation process. Prior to the introduction of ring C, however, it is highly desirable to remove the cyclohexanone carbonyl in the molecule. Towards this end, the hydroxy group of **95** was protected as a silyl ether by treatment with trimethylsilyl chloride in the presence of triethylamine and DMAP in methylene chloride at room temperature for 7 h. The resulting diketone **110** was selectively reduced to a pair of epimeric hydroxy ketones **111** in virtually quantitative yield using lithium tri-*tert*-butoxyaluminum hydride in ether. The ratio of the two epimers was found to be 85:15 when the reaction was carried out at room temperature. At -30°C, an improved stereoselectivity was observed leading to the formation of a 95:5 epimeric mixture. The epimers were

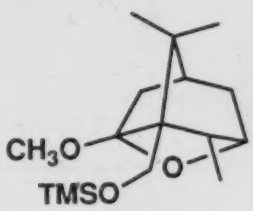
readily separable by flash chromatography. The major epimer was shown to be less polar on silica gel, and therefore assigned as **111a** with an *endo* hydroxy group because its polarity could be decreased by the formation of intramolecular hydrogen bond with the carbonyl oxygen. This was subsequently proved by the formation of cyclic acetal **138**.



110



111a R =H, R' = OH
111b R = OH, R' = H

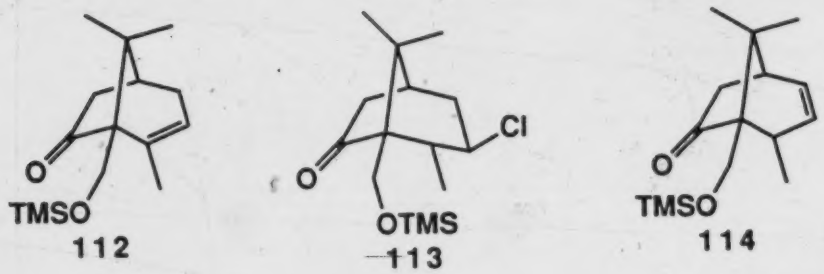


138

2. Aldol approach

According to our synthetic plan by Routes 2 and 3, the hydroxy group in compound **111a** was to be eliminated to form the carbon-carbon double bond present in the target molecule. Although another carbon-carbon double bond will be formed later in the expected intermediates **99** and **100** (Scheme 21), selective reduction of this conjugated carbon-carbon double bond could be achieved by known methods such as dissolving metal reduction. Therefore, we decided to carry out dehydration to introduce the double bond functionality at this stage.

Compound **111a** was treated with thionyl chloride[17] and pyridine in methylene chloride at room temperature for 24 h. The reaction gave dehydration product **112** in a 87% yield, along with a 11% yield of substitution product **113**. Interestingly, when the reaction was carried out using triethylamine instead of pyridine, the major product formed was **114** with a disubstituted carbon-carbon double bond. The dehydration reaction was also performed using phosphorus oxychloride and pyridine in methylene chloride. At room temperature, a mixture consisting of four parts of olefin **112** and one part of chloride **113** was produced in high yield after 19 h. Similar results were obtained at 0°C after a longer reaction period.



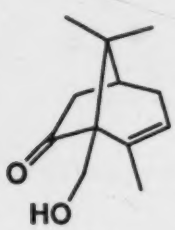
The structure of compound **112** was readily established by its ^1H nmr spectrum, in which three methyl singlets were observed at δ 1.00, 1.14 and 1.80 , along with a broad singlet (δ 5.50) for the vinylic proton. The structural assignment was supported by the ir spectrum, which showed no hydroxy absorption but a carbonyl absorption band at 1731 cm^{-1}. The required molecular formula of $C_{15}H_{26}O_2Si$ was confirmed by the molecular ion peak at 266.1698 in the mass spectrum. The strongest evidence for the formation of chloride **113** was the molecular ion peaks

at 304.1451 and 302.1469, in the mass spectrum indicating a molecular formula of $C_{15}H_{27}ClO_2Si$. The stereochemistry at C-3 and C-4 was uncovered by the ^1H nmr spectrum, in which a doublet of doublets of doublets at δ 3.65 with two axial-axial coupling constants of 11 Hz each and one axial-equatorial coupling constant of 7 Hz was observed for the proton at C-3. The mass spectrum of compound **114** displayed a molecular ion peak at 266.1696, indicating that this compound was isomeric with **112**. The ^1H nmr spectrum indicated the presence of a disubstituted double bond showing two doublets of doublets at δ 5.92 and 5.45, coupled to each other with a coupling constant of 9 Hz. The former was found to further couple with the C-4 proton at δ 2.66 (J = 2 Hz), while the latter with the C-1 proton at δ 2.12 (J = 7 Hz).

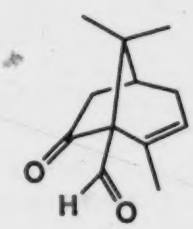
exo-Alcohol **111b** was also subjected to dehydration with thionyl chloride in methylene chloride at room temperature in the presence of pyridine. The reaction was found to be complete after 10 h, but gave mainly an epimeric mixture of the corresponding chlorides (~70% yield) and only a trace amount of the desired olefin **112** (~10% yield). Thus *exo*-alcohol **111b** could not serve as an effective intermediate.

Deprotection of the hydroxy group was readily achieved by treatment of compound **112** with tetrabutylammonium fluoride in tetrahydrofuran at room temperature for 24 h. The resulting primary alcohol **115** was subjected to oxidation using Swern's modification[18] of the Moffatt oxidation. Alcohol **115** was treated sequentially with a solution of oxalyl chloride and dimethyl sulfoxide (DMSO) in methylene chloride and then

with triethylamine over a temperature range of -78°C to 20°C. Aldehyde **99** thus obtained in 81% yield showed, in the ^1H nmr spectrum, a one-proton singlet for the aldehyde proton and three methyl singlets at δ 1.05, 1.12 and 1.69. In agreement with the structural assignment, the ir spectrum displayed two carbonyl absorption bands at 1717 and 1735 cm^{-1} for the aldehyde group and the five-membered ring ketone, respectively.



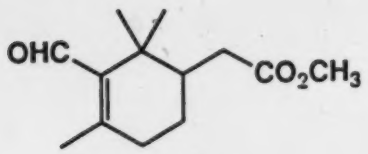
115



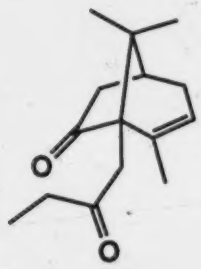
99

The conversion of aldehyde **99** to the projected key intermediate **100** for Route 3 requires the extension of the aldehyde group by a three-carbon unit. Towards this end, compound **99** was treated with 1-nitropropane[15] and potassium carbonate in methanol. The reaction gave a product in 68% yield. The molecular formula of $C_{13}H_{20}O_3$ was suggested for this compound by the molecular ion peak at 224.1410 in the mass spectrum. The ir spectrum showed carbonyl absorption bands at 1737 and 1671 cm^{-1} characteristic of ester and α,β-unsaturated aldehyde, respectively. In the ^1H nmr spectrum, four methyl singlets at δ 3.55, 1.95, 1.12 and 0.90 and an aldehyde singlet at δ 10.00 were observed. On the basis of these spectral data, the structure of this product was deduced as **116**. This compound could have arisen from the addition of

methoxide ion to the ketone carbonyl of **99** followed by a retro-aldol type fragmentation. Other conditions were attempted for the addition of 1-nitropropane to aldehyde **99**. When sodium hydroxide was used as a base, fragmentation product **116** was again formed as the major product. On the other hand, using triethylamine as a solvent, with or without the presence of sodium hydride, was shown to be ineffective.

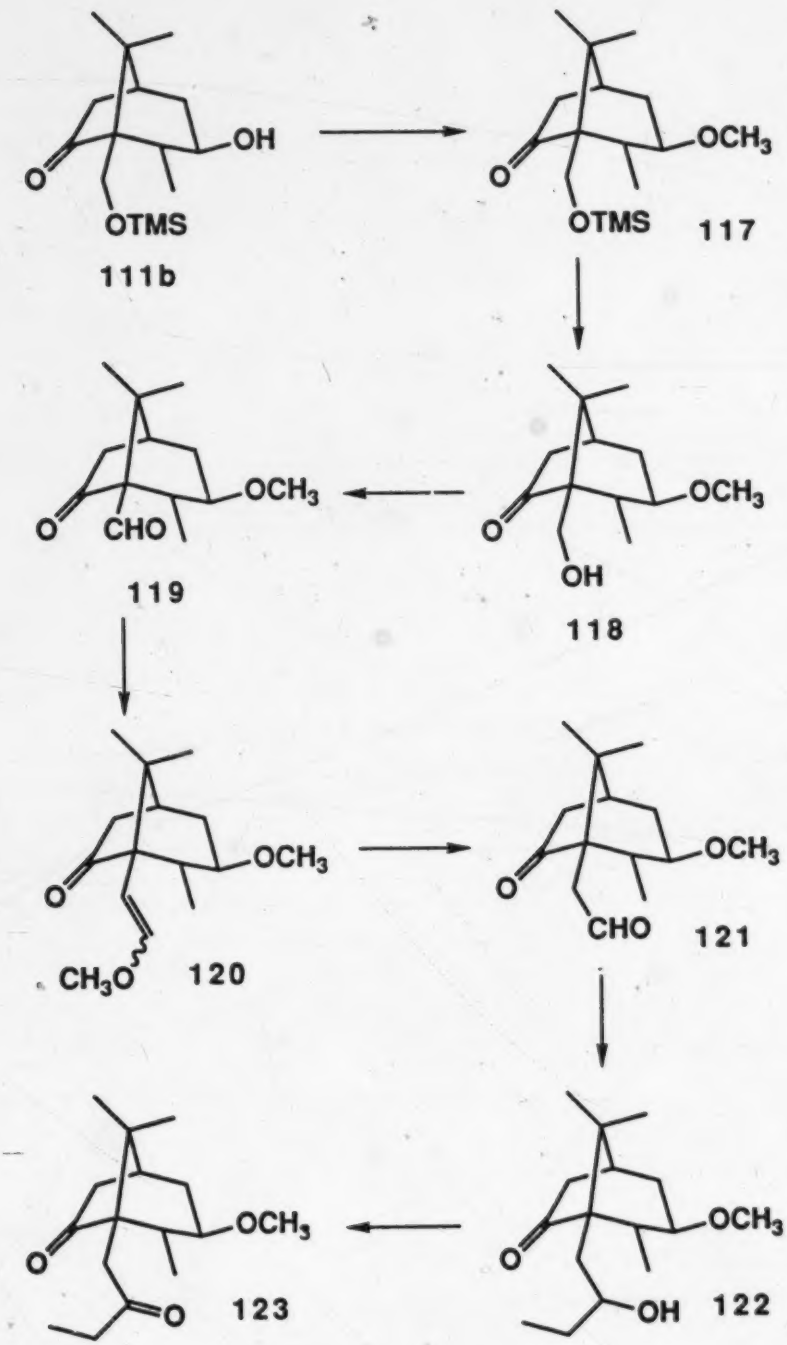


116



100

In another approach (Scheme 22) which called for a stepwise installation of the required three-carbon unit, alcohol **111b** was used as a model. After the hydroxy group in **111b** was protected by methylation with iodomethane and sodium hydride in dimethoxyethane (**111b→117**), the silyl group was removed by treatment with potassium fluoride in refluxing methanol for 4 h. Swern oxidation of alcohol **118** thus formed was carried out subsequently to give aldehyde **119**. The structural assignments of compound **117**, **118**, and **119** were readily made on the basis of their spectral data. For example, the ^{1}H nmr spectrum of methyl ether **117** displayed three methyl singlets at δ 3.33, 1.23 and 0.96, a methyl doublet (J = 6 Hz) at δ 0.93, and a nine-proton singlet at δ 0.08


OH
OTMS
111b
OCH3
OTMS
117
OCH3
OH
118
OCH3
CHO
119
OCH3
CH3O
120
OCH3
CHO
121
OCH3
OH
122
OCH3
O
123

Scheme 22.

for the trimethylsilyl group, while the ir spectrum showed a ketone carbonyl absorption at 1734 cm^{-1}. As another example, the presence of the aldehyde functional group in compound **119** was evident from the singlet at δ 9.80 in the ^1H nmr spectrum.

Keto aldehyde **119** was subjected to Wittig reaction with methoxymethyl-triphenylphosphonium chloride and *n*-butyllithium in tetrahydrofuran at room temperature. The reaction proceeded with complete regioselectivity and a pair of geometrical isomers (1:1) of enol ether **120** was obtained in high yield. These isomers were partially separated by flash chromatography on silica gel. In the ^1H nmr spectrum of the less polar isomer, four methyl singlets at δ 3.49, 3.32, 1.16 and 0.86 were observed along with two one-proton doublets at δ 5.92 and 4.00 coupled to each other with a coupling constant of 7.5 Hz. According to the chemical shifts and the small coupling constant of the latter two olefinic signals,[19] a *cis* stereochemistry was assigned to this isomer. In the ^1H nmr spectrum of *trans*-**120**, the corresponding signals appeared at δ 3.53, 3.31, 1.10 0.82, 6.47 (J = 13 Hz), and 4.36 (J = 13 Hz).

Hydrolysis of enol ethers **120** in a mixture of 35% perchloric acid and ether (1:1) resulted in the formation of aldehyde **121** (91% yield). The ^1H nmr spectrum of this product displayed two doublets of doublets at δ 2.84 and 2.25 coupled to each other with a geminal coupling constant of 16 Hz. Each of these signals was found to further couple with the doublet of doublets (J = 2, 4 Hz) at δ 9.90 due to the aldehyde proton.

Therefore, the presence of the newly incorporated 2-oxoethyl moiety was confirmed.

The remaining two carbons were introduced to aldehyde **121** by a Grignard reaction using ethylmagnesium bromide in tetrahydrofuran. The resulting keto alcohol **122** was oxidized to diketone **123** using Swern's method. The structure of the product was confirmed by the following spectral data. In the ir spectrum, two intense absorption bands at 1732 and 1709 cm^{-1} were observed for the five-membered ring carbonyl and the acyclic carbonyl group, respectively. A molecular ion peak at 266.1879 in the mass spectrum was consistent with the required molecular formula of $C_{16}H_{26}O_3$. The presence of the 2-oxobutyl side-chain was evident from the ^1H nmr spectrum which displayed two one-proton doublets at δ 2.98 and 2.30 coupled to each other with a large geminal coupling constant of 18 Hz and a two-proton quartet (J = 7.5 Hz) at δ 2.48 which was found to mutually couple with the triplet at δ 1.03.

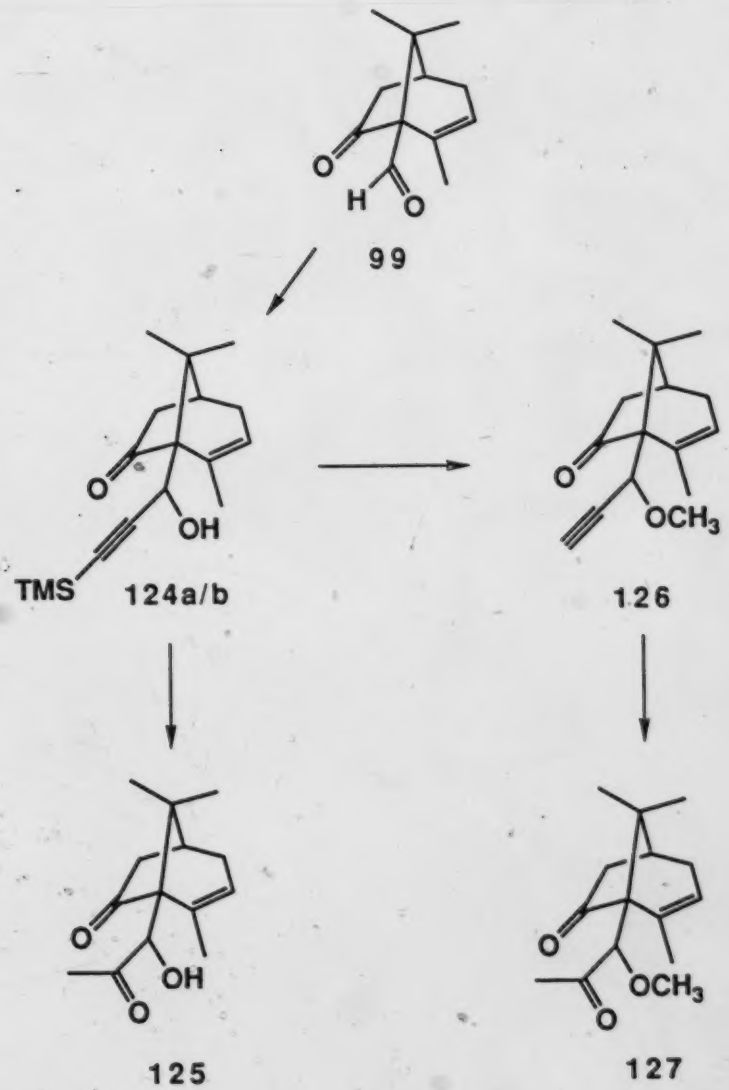
For the construction of the tricyclic skeleton of α-patchoulene by an intramolecular aldol condensation process, two more bicyclic diketones **125** and **127** were prepared from compound **99** *via* the synthetic sequence as shown in Scheme 23. Addition of trimethylsilyl-acetylenyllithium to **99** resulted in a pair epimers **124a** and **124b** in 1:3 ratio and a total yield of 91%. The major isomer **124b** was converted to methyl ketone **125** in 91% yield by hydrolysis of the acetylene group with aqueous sulfuric acid in methanol under the catalysis of mercury(II)

chloride. The minor isomer was used for the preparation of diketone **127** by a two-step procedure. Methylation with sodium hydride and iodomethane followed by hydrolysis of the triple bond gave diketone **127** in an overall yield of 81%. In an attempt to remove the α-hydroxy group, compound **125** was treated with zinc dust[20] in acetic acid at room temperature. These condition were found to be ineffective and the starting material was recovered intact. On the other hand, when the reaction mixture was heated under reflux, unidentifiable products were formed.

The structures of compounds **125** and **127** were established by their spectral data. The mass spectrum of the former compound displayed the molecular ion peak at 236.1416 in agreement with the molecular formula of $C_{11}H_{20}O_3$. The ir spectrum showed the hydroxy absorption at 3408 cm^{-1} and the carbonyl absorption at 1709 cm^{-1}. In the ^1H nmr spectrum, a three-proton singlet at δ 2.34 was observed for the methyl ketone moiety, along with a doublet at δ 4.98, which was found to couple with the hydroxy proton signal at δ 3.24 with a coupling constant of 4 Hz. Diketone **127** showed, in the ^1H nmr spectrum, five methyl singlets at δ 3.33, 2.27, 1.78, 1.13 and 0.92, and a one-proton singlet at δ 4.33 for the proton adjacent to the methoxy group.

Compounds **123**, **125**, and **127** were individually subjected to intramolecular aldol condensation under a variety of conditions including potassium carbonate in methanol at 20°C and in refluxing acetone, sodium hydroxide in methanol, and *p*-toluenesulfonic acid in refluxing

benzene. Unfortunately, all the attempts made proved to be unsuccessful. Under the basic conditions, the starting materials were recovered in most of the cases examined. Under the acidic conditions, decomposition of the starting material in each case was observed. In no case, the desired cyclization product was detected.



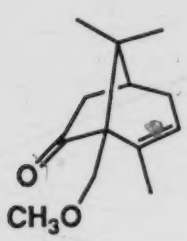
Scheme 23.

For the other aldol approach (Route 2), it was necessary to replace the cyclopentanone carbonyl of keto silyl ether **112** with an acetyl group. As expected, this highly hindered ketone carbonyl exerted poor reactivity with a number of nucleophiles attempted. Treatment of **112** with trimethylsilylacetylenyllithium, trimethylsilylacetylenylcerium(III) chloride,[21] acetylenylmagnesium bromide[22] and vinyllithium resulted in recovery of the starting material in most cases and the removal of the trimethylsilyl group in the others. The steric hindrance of the carbonyl group could be partly due to the adjacent bulky trimethylsilyl group. It is conceivable that replacement of this hydroxy protecting group with a smaller one could reduce the unfavorable steric effect thereby the reactivity of the carbonyl could be improved.

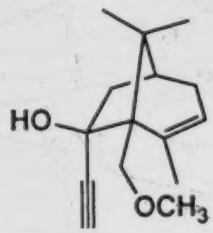
This expectation was supported experimentally by the successful addition of acetylenylmagnesium bromide[22] to ketone **128**, which was produced by methylation of compound **115** with iodomethane and sodium hydride in dimethoxyethane. When ketone **128** was treated with acetylenylmagnesium bromide, freshly prepared *in situ* from acetylene gas and ethylmagnesium bromide, a pair of epimers **129** and **130** were obtained in *ca* 1:1 ratio. For unknown reasons, however, the yield was not highly reproducible ranging from 30% to 85%.

In the mass spectrum of compound **129**, the molecular ion peak at 234.1608 indicated the molecular formula of $C_{15}H_{22}O_2$. The ir spectrum showed a hydroxy absorption at 3480 cm^{-1}, a triple bond stretching absorption band at 2100 cm^{-1} and an absorption band at 3300 cm^{-1}

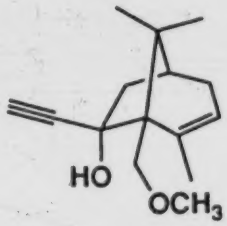
corresponding to the stretching of the carbon-hydrogen bond of a terminal alkyne. The ^{1}H nmr spectrum displayed a singlet at δ 2.38 for the acetylenic proton and four methyl singlets at δ 3.37, 1.90, 1.27 and 0.98.



128



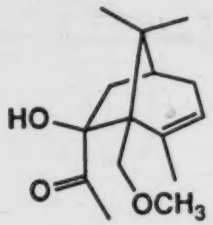
129



130

Compound **130** was shown to be epimeric with **129** by a comparison of their mass spectra. This was confirmed by the ir spectrum of **130**, which displayed absorption bands at 3480, 3300 and 2360 cm^{-1} similar to those observed for compound **129** . In the ^{1}H nmr spectrum, singlets at δ 2.66 (1H), 3.35 (3H), 1.80 (3H), 1.28 (3H) and 1.08 (3H) were observed.

The stereochemistry of these epimeric addition products could not be clearly defined based on the above spectral data. The configuration of the newly generated chiral center in each case was disclosed after the hydrolysis as follows. Compounds **129** and **130** were individually hydrolyzed in aqueous methanol in the presence of mercury(II) chloride and hydrochloric acid in order to prepare the corresponding methyl ketones **131** and **132**.



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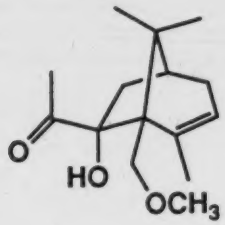
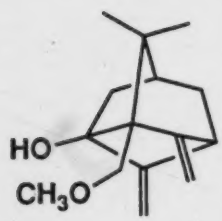
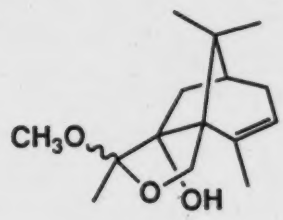


132

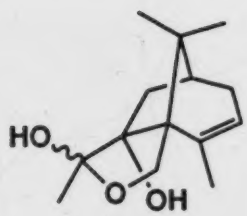
From compound **129**, a single product was obtained in high yield. However, the ir spectrum of this compound showed a strong hydroxy absorption at 3400 cm^{-1} and the absence of the expected carbonyl band.



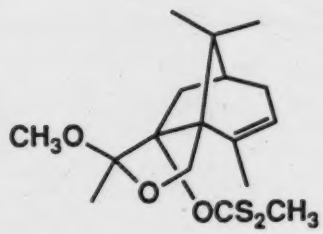
133



134

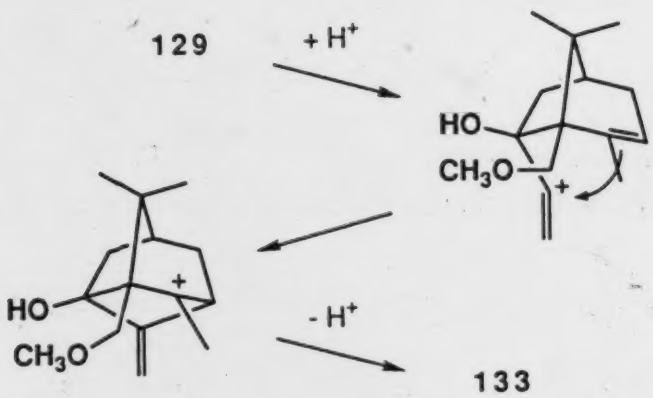


135



136

Clearly, this product was not the desired methyl ketone **131**. The assigned structure **133** for this compound was suggested by the ^1H nmr spectrum, which showed four one-proton singlets at δ 4.86, 4.75, 4.58 and 4.43 characteristic of protons attached to terminal vinylic double bond, and the absence of the acetylenic proton signal present in the spectrum of the starting material. Furthermore, only three methyl signals were observed, one (δ 3.33) for the methoxy group and others (δ 1.08 and 0.94) for the geminal dimethyl. These data indicated the formation of two disubstituted terminal double bonds during the reaction at the expense of the vinylic methyl group and the triple bond. In conjunction with the mechanistic consideration shown in Scheme 24, the structure of the unexpected product was deduced as shown in formula **133**. This assignment was confirmed by the mass spectrum showing the required molecular ion peak at 234.1616 as well as by the ^{13}C nmr (APT) spectrum which clearly indicated the presence of four sp^2 carbons.



Scheme 24

The *exo*-adduct **130** was also subjected to hydrolysis with mercury(II) chloride and aqueous sulfuric acid in methanol. Three products were formed in a ratio of 1:3:3 and in a total yield of 88%. Two of these compounds (the minor and one of the major) were identified as a pair of epimeric cyclic acetal **134** according to their spectral data. The molecular ion peak at 252.1717 in the mass spectrum of the major epimer was consistent with the molecular formula of $C_{12}H_{24}O_3$. The ir spectrum of each epimer showed hydroxy bands at 3500 and 3300 cm^{-1} and the absence of carbonyl absorption. The ^1H nmr spectra of the epimers were similar to each other. The major isomer showed five methyl singlets at δ 3.30, 1.56, 1.40, 1.04 and 0.95 and one vinylic signal at δ 5.40 as a broad singlet. Another singlet at δ 4.00, which was suppressed on addition of deuterium oxide, was assigned to the hydroxy proton. The spectrum of the minor epimer showed seven signals at δ 3.32, 1.65, 1.35, 1.15, 1.00, 5.52 (broad), and 2.80 for the corresponding protons. The third product showed, in the ^1H nmr spectrum, four methyl singlets at δ 1.04, 1.06, 1.54, and 1.68, a broad singlet at δ 5.60 for the vinylic proton, and two D_2O exchangeable protons at δ 3.60 and 5.10. These spectral data strongly suggested that the compound was a hemiacetal, for which structure **135** could be readily assigned. This assignment was confirmed by its conversion to the epimeric acetals **134** with mercury(II) chloride in methanol in the presence of sulfuric acid.

Acetals **134** could be considered as the masked ketone **132**. In further exploration of Route 2 to the target molecule, the major acetal **134** was

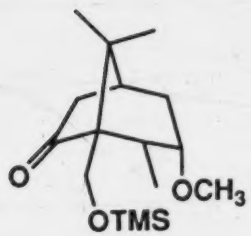
treated with sodium hydride, iodomethane and carbon disulfide in dimethoxyethane at room temperature,[23, 24] in an attempt to remove the hydroxy group *via* its xanthate. Xanthate **136** thus obtained in good yield showed, in the mass spectrum, a molecular ion peak at 342.1325 corresponding to the required molecular formula of $C_{17}H_{26}O_3S_2$. In the ^1H nmr spectrum, six methyl singlets were displayed at δ 3.21, 2.48, 1.72, 1.70, 1.08, and 0.99 in agreement with the assigned structure.

Xanthate **136** was subsequently subjected to reduction with tributyltin hydride under the catalysis of azobisisobutyronitrile (AIBN) in refluxing toulene.[25] Unfortunately, the reaction did not lead to the formation of the desired product and a complex mixture was invariably formed in several attempts.

3. McMurry approach

Because it would be difficult to selectively reduce a tetra-substituted carbon-carbon double bond, which would be formed in the later stage of the projected McMurry approach (see Scheme 19), in the presence of a tri-substituted one, enone alcohol **115** was not regarded as a suitable precursor for this approach. Instead, keto alcohol **111a** was used as the starting point. Methylation of **111a** with iodomethane and sodium hydride gave, interestingly, the cyclic acetal **138** (92% yield). The ir spectrum of this compound did not show any carbonyl absorption and the mass spectrum displayed a molecular ion peak at 298.1966 corresponding to the correct molecular formula of $C_{16}H_{30}O_3Si$. The

structural assignment was further confirmed by the ^{1}H nmr spectrum, in which, four methyl signals were displayed at δ 1.03 (d), 1.10, 1.19, and 3.39, along with an intense singlet at δ 0.08 (9H) for the trimethylsilyl group.



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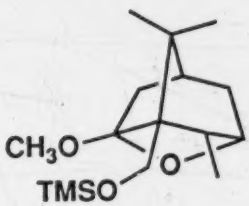
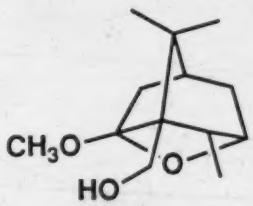


138

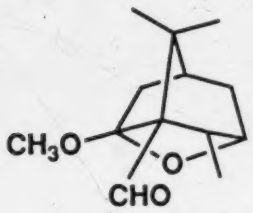


139

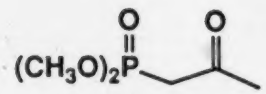
After removal of the trimethylsilyl group in compound **138** with potassium fluoride in refluxing methanol, alcohol **139** was oxidized using Swern's method. Aldehyde **140** thus obtained showed, in the ir spectrum, absorption bands at 2856 and 1707 cm^{-1} due to the aldehyde group. In the ^{1}H nmr spectrum, four methyl signals, three singlets (δ 3.54, 1.16, and 1.09) and one doublet (δ 1.03, J = 6.5 Hz), were observed, along with a singlet at δ 9.82 for the aldehyde proton.

Compound **140** was subjected to Horner-Emmons reaction using dimethyl acetonylphosphone (**141**)[26] in order to install directly the required acetone unit. Unfortunately, the desired product was not formed under a variety of reaction conditions including sodium hydride in DMSO at room temperature and butyllithium in tetrahydrofuran, at a temperature range of *ca.* 20-70°C. In most of the experiments, the starting material

was recovered intact, apparently due to the poor reactivity of both the reactant and the reagent.



140



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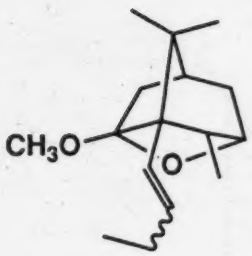
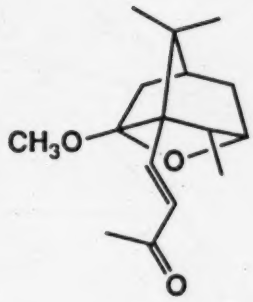


142



143

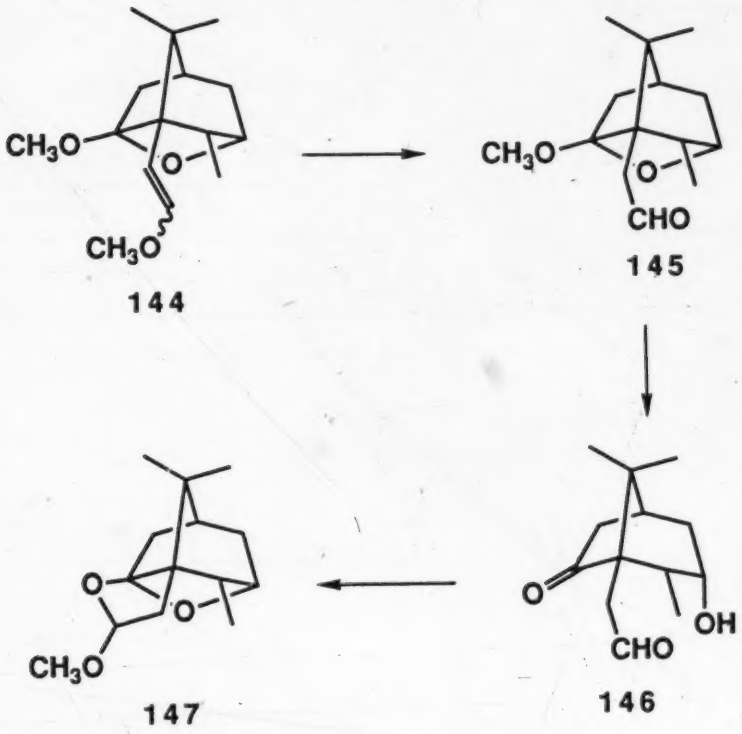
Alternatively, the required three-carbon unit was introduced using a more reactive phosphorus ylide triphenyl-1-propylenephosphorane, prepared from triphenylpropylphosphonium bromide and *n*-butyllithium.[27, 28] Treatment of aldehyde **140** with this Wittig reagent in tetrahydrofuran at room temperature gave rise to compound **142**, which showed a molecular ion peak at 250.1931 in the mass spectrum in agreement with the molecular formula of $C_{16}H_{26}O_2$. The ^1H nmr spectrum displayed a complex signal at δ 5.44 for two vinylic protons and five methyl signals,

including three singlets at δ 3.45, 1.13 and 0.87, one doublet (J = 6.5 Hz) at δ 0.97 and one triplet (J = 7.5 Hz) at δ 1.03.

The transformation of olefin **142** to the desired enone **143** requires the incorporation of an oxygen to the 2° allylic carbon. Thus, olefin **142** was treated with selenium dioxide in ethanol in the presence of *tert*-butyl hydroperoxide at room temperature.[29] Under these conditions, the starting compound was recovered intact. When the allylic oxidation was carried out with selenium dioxide in acetic acid at 90°C,[30] a distinct product was formed. However, a spectroscopic analysis clearly indicated that it was not the desired oxidation product. Other methods such as pyridinium chlorochromate (PCC) on aluminium oxide,[31] were also attempted to no avail.

In order to prepare diketone **96** to test the viability of the cyclization under McMurry reaction conditions, a multistep procedure was applied. Although this procedure was obviously not efficient, it seemed to be a more reliable way to construct the required key intermediate for cyclization in the McMurry approach. In this preparation, compound **138** was subjected to one-carbon extension with methoxymethylene-triphenylphosphorane to give compound **144** in 92% yield. Subsequent treatment of **144** with 35% perchloric acid in ether afforded the desired aldehyde **145**. The yield (62%) of this compound, however, was rather disappointing due to the formation, likely *via* **145** by the mechanistic pathway shown in Scheme 25, of by-products **146** and **147** which were produced in substantial quantity. Several attempts made to suppress the

generation of these by-products, including the use of trimethylsilyl chloride and sodium iodide,[32] were fruitless.

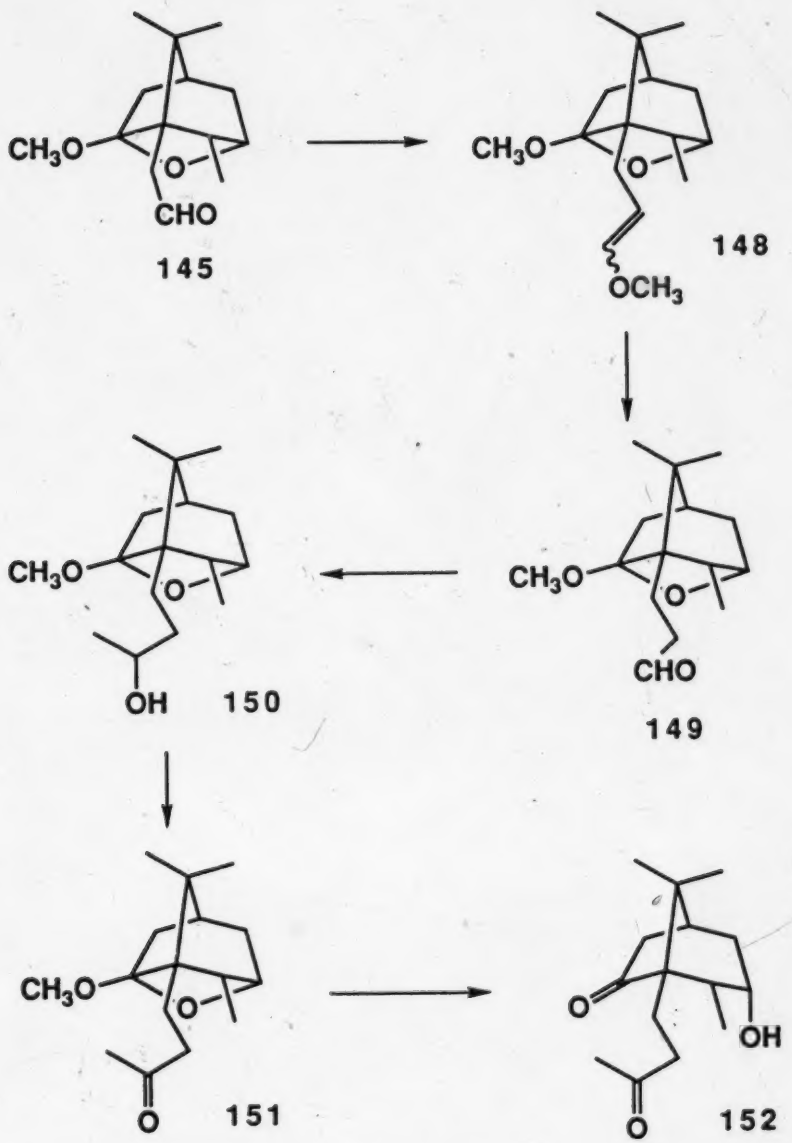


Scheme 25

For the preparation of diketone **97**, a two carbon extension was attempted on compound **145** with 1-methoxyethylenetriphenylphosphorane in tetrahydrofuran,[33] but the desired Wittig reaction did not take place at various temperatures. Consequently, a multistep sequence (Scheme 26) was adapted. Aldehyde **145** was converted to its homolog **149** in 53% yield *via* enol ether **148** by treatment with methoxymethylenetriphenylphosphorane followed by acid catalyzed

hydrolysis. Addition of methyllithium followed by Swern oxidation of the resulting alcohol **150** gave methyl ketone **151**, which showed a carbonyl absorption at 1715 cm^{-1} in the ir spectrum. The molecular formula of $C_{16}H_{26}O_3$ was confirmed by the molecular ion peak at 266.1882 in the mass spectrum. In the ^1H nmr spectrum, five methyl signals, including four singlets at δ 3.43, 2.17, 1.15 and 1.04 and one doublet (J = 7 Hz) at δ 0.97 were observed, along with two doublets of doublets of doublets at δ 2.50 (J = 16, 12, 6.5 Hz) and 2.31 (J = 16, 11, 4 Hz) for the α-protons of the carbonyl.

Diketo alcohol **152** was obtained from compound **151** by treatment with 72% perchloric acid in diethyl ether. The structure of diketo alcohol **152** was established by its spectral data. In the ir spectrum, intense absorption bands at 3440, 1734, and 1715 cm^{-1} were displayed for the hydroxy and carbonyl groups, respectively. The molecular formula of $C_{15}H_{24}O_3$ was evident from the molecular ion peak at 252.1723 in the mass spectrum. In the ^1H nmr spectrum, four methyl signals, including three singlets at δ 2.15, 1.18 and 0.95 and one doublet (J = 7.5 Hz) at δ 0.93 were displayed. The methyl doublet was found to couple to a quartet at δ 2.32, which was attributed to the proton at C-4. Four doublets of doublets of doublets at δ 2.42 (J = 16, 12, 6 Hz), 2.27 (J = 16, 11, 4.5 Hz), 2.05 (J = 19, 12, 4.5 Hz) and 1.49 (J = 19, 11, 6 Hz), were attributable to the methylene protons of the side-chain. The doublet at δ 2.67 and the doublet of doublets of doublets at δ 2.25, coupled to each other with a large geminal coupling constant of 18 Hz, were assigned to the *endo* and *exo* protons at C-7, respectively.


CH3O
O
CHO
145
CH3O
O
OCH3
148
CH3O
O
CHO
149
CH3O
O
OH
150
CH3O
O
O
151
O
OH
O
152

Scheme 26.

Similarly, the signals for the *endo* and *exo* protons on C-2 appeared as a doublet (J = 14 Hz) at δ 2.32 and a doublet of doublets of doublets (J = 14, 3, 1 Hz) at δ 1.81. A W-coupling (J = 1 Hz) was observed for the two *exo* protons at C-2 and C-7. These protons were also individually coupled with the C-1 bridgehead proton which appeared at δ 1.88 as a doublet of doublets (J = 3, 7 Hz). Two other signals at δ 4.00 and 1.24 as broad singlets were due to the C-3 proton and the hydroxy proton, respectively.

Having diketone **152** in hand, the McMurry cyclization was attempted. This compound was subjected to treatment with Ti(0), freshly generated by the reduction of titanium trichloride with potassium metal. Both tetrahydrofuran and dimethoxyethane were used as the solvent and reflux temperature was applied as generally required for this type of coupling reaction.[34] To our disappointment, in all attempts, severe loss of material was encountered and the desired cyclization product was not detected.

4. Conclusion

An extensive study on the total synthesis of α-patchoulene (**74**) has been carried out, starting from 10-camphorsulfonic acid. A highly efficient transformation of this compound to the bicyclic diketo alcohol **95**, which contains the A/B ring system of the synthetic target, has been developed using a six-step reaction sequence in which the skeletal rearrangement of **109**→**95** serves as a key operation. For the construction of the C ring,

three synthetic routes were devised based on intramolecular aldol condensation reaction and McMurry's diketone coupling reaction. Each of these approaches has been examined and advance intermediates prepared. Unfortunately, at the present time, none of these projected synthetic routes proved to be viable to bring about ring C formation. The lack of success in the attempted aldol cyclization of compounds **123**, **125**, and **127** might be due to the steric conjestion of the neopentyl ketone carbonyl. In continuation of the synthetic studies, further exploration of the McMurry approach should be carried in several fronts. Although the cyclization of diketo alcohol **152** could not be effectively induced as shown by the current work, its derivative with a protected hydroxyl such as **96** could take a different course of the reaction. Furthermore, recent studies have shown that $TiCl_3$/K/graphite[35] and $TiCl_3(DME)_{1.5}$/Zn-Cu[36] are superior reagents for the coupling of dicarbonyl compounds. These reagents may prove to be effective as well for our synthetic purpose.

EXPERIMENTAL

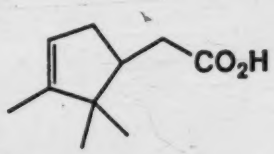
General

For general remarks see the experimental section of Chapter I of this thesis.

Materials

Methanol was purified by refluxing and distilling over magnesium turnings. Other solvents were purified by the procedures described in the experimental section of Chapter I of this thesis. (±)-10-Camphorsulfonic acid sodium salt was obtained from Aldrich Chemical Company. Triphenylpropylphosphonium bromide was prepared by the reaction of 1-bromopropane with triphenylphosphine in refluxing benzene.

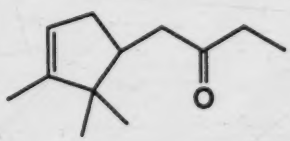
Campholenic acid (101)



A mixture of potassium hydroxide (~85% pure, 300 g, ~4.5 mol) and sodium hydroxide (150 g, ~3.7 mol) was fused in a porcelain casserole with a Bunsen burner. The flame was removed and (±)-10-camphorsulfonic acid sodium salt (100 g, 0.39 mol) was added slowly

with vigorous stirring over a period of 20 min. The brown solid was heated again with a Bunsen burner until it turned into a yellowish syrup. After the molten mass was cooled to room temperature, ice and water (200 mL) were added slowly to the hard cake. The resulting mixture was acidified with 12 *N* aqueous hydrochloric acid and cooled by addition of ice. The resulting mixture was extracted with methylene chloride (3 x 500 mL). The extracts were washed with water, dried, filtered, and concentrated. The crude material was distilled at 100-110°C / 0.5 mmHg to give carboxylic acid **101** (50 g, 76% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.80 (s, 3H, -CH_3), 1.00 (s, 3H, -CH_3), 1.62 (d, 3H, J = 2 Hz, vinylic CH_3), 1.7-2.6 (complex, 5H), 5.26 (bs, 1H, =CH-), and 11.75 (bs, 1H, -COOH); ir 3500 (COOH) and 1718 cm^{-1} (C=O); ms M$^+$ 168.1152 (calcd. for $C_{10}H_{16}O_2$: 168.1150); Anal. Calcd. for $C_{10}H_{16}O_2$: C 71.38, H 9.59; Found: C 71.42, H 9.63.

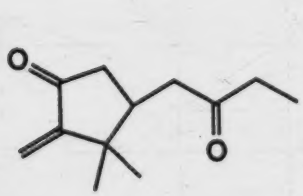
1,5,5-Trimethyl-4-(2-oxobutyl)cyclopentene (102)



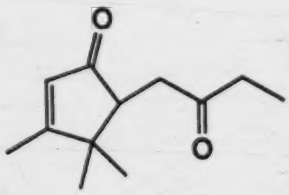
To a solution of carboxylic acid **101** (6.427 g, 38.2 mmol) in ethyl ether (60 mL) and tetrahydrofuran (30 mL) under an argon atmosphere, was added lithium hydride (95% pure, 0.319 g, 38.2 mmol). The reaction mixture was stirred for 24 h. Then a solution of ethyllithium, which was freshly prepared from the reaction of bromoethane (8.28 g, 76.4 mmol) with excess metal lithium (~1.0 g) in petroleum ether (30 mL) followed by

addition of benzene (150 mL), was added to the flask containing the lithium carboxylate. After stirring for 2 h, the reaction mixture was carefully poured into an ice-cold 1 *N* aqueous hydrochloric acid (200 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 30 mL). The organic extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (1:19) gave ketone **102** (6.27 g, 34.8 mmol, 91% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.75 (s, 3H, -CH_3), 0.93 (s, 3H, -CH_3), 1.00 (t, 3H, J = 7 Hz, -CH_2CH_3), 1.57 (bs, 3H, vinylic CH_3), 2.00 (complex, 7H), and 5.20 (bs, 1H, =CH-); ir 1702 cm^{-1} (C=O); ms M$^+$ 180.1512 (calcd. for $C_{12}H_{20}O$: 180.1514); Anal. Calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18; Found: C 80.27, H 11.23.

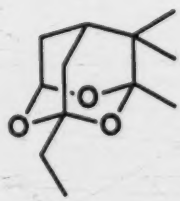
3,3-Dimethyl-2-methylidene-4-(2-oxobutyl)cyclopentanone (103), 3,4,4-trimethyl-5-(2-oxobutyl)-2-pentenone (104), and 1-ethyl-3,4,4-trimethyl-2,8,10-trioxatricyclo[3.3.1.1^{3,7}]-decane (105)



103



104

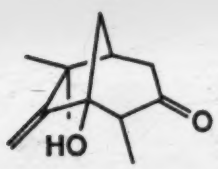


105

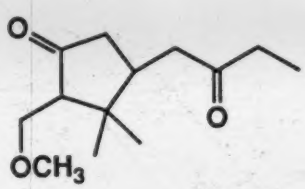
A solution of ketone **102** (28.0 g, 155 mmol), acetic anhydride (22 mL, 232 mmol), pyridine (25 mL, 310 mmol), TPP (30 mg) and DMAP (30 mg) in methylene chloride (1200 mL) was irradiated with four 200 W tungsten lamps for 10 h. During this period a moderate stream of oxygen was bubbled through the solution. After stirring for an additional period of 12 h, the reaction mixture was washed with 1 *N* aqueous hydrochloric acid (2 x 500 mL), saturated sodium bicarbonate (2 x 500 mL) and brine. The organic layer was dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with a solution of 20% ether in hexane gave α,β-unsaturate ketone **103** (16.71 g, 86 mmol, 55% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.02 (s, 3H, -C**H**$_3$), 1.06 (t, 3H, *J* = 7.5 Hz, -CH_2C**H**$_3$), 1.24 (s, 3H, -C**H**$_3$), 2.3-2.7 (complex, 7H), 5.22 and 5.98 (s, 1H each, =C**H**$_2$); ir 1724 (C=O), 1640 (C=O), and 1633 cm^{-1} (C=C); ms M$^+$ 194.1305 (calcd. for $C_{12}H_{18}O_2$: 194.1307). Further elution with solutions of 5%, 15%, and 25% ether in hexane gave the starting material **102** (2.54 g, 14.1 mmol, 9% recovery), by-product **104** (1.32 g, 6.8 mmol, 4.4% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.96 (s, 3H, -C**H**$_3$), 1.09 (t, 3H, *J* = 7 Hz, -CH_2C**H**$_3$), 1.27 (s, 3H, -C**H**$_3$), 2.03 (s, 3H, vinylic C**H**$_3$), 2.3-2.9 (complex, 5H), and 5.84 (s, 1H, =C**H**-); ^{13}C nmr (APT, 300 MHz, $CDCl_3$) δ 8.35 (q), 36.59 (t), 14.87 (q), 23.63 (q), 26.39 (q), 36.59 (t), 39.70 (t), 46.25 (s), 53.84 (d), 128.17 (d), 185.14 (s), 208.81 (s), and 210.52 (s); ir 1701 (C=O) and 1619 cm^{-1} (C=O); ms M$^+$ 194.1307 (calcd. for $C_{12}H_{18}O_2$: 194.1307); and **105** (0.54 g, 2.55 mmol, 1.6% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.5 Hz, -CH_2C**H**$_3$), 1.11 (s, 3H, -C**H**$_3$), 1.15 (s, 3H, -C**H**$_3$), 1.25 (s, 3H, -C**H**$_3$), 1.59 (q, 2H, *J* = 7.5 Hz, -CH_2C**H**$_3$), 1.80 (dd, 1H, *J* = 12, 3 Hz, C-9

CH_2), 1.86 (ddd, 1H, J = 12, 2, 2 Hz, C-6 CH_2), 2.17 (ddd, 1H, J = 12, 3, 3 Hz, C-9 CH_2), 1.85(m, 1H, C-5 CH), 2.27 (dddd, 1H, J = 12, 2.5, 2.5, 3 Hz, C-6 CH_2), and 5.26 (dd, 1H, J = 2.5, 2 Hz, C-7 CH); no ir absorption for either C=O or OH; ms M^+ 212.1413 (calcd. for $C_{12}H_{20}O_3$: 212.1412).

1-Hydroxy-7-methylidene-2,6,6-trimethylbicyclo[3.2.1]octan-3-one (106) and 2-methoxymethyl-3,3-dimethyl-4-(2-oxobutyl)-cyclopentanone (107)



106

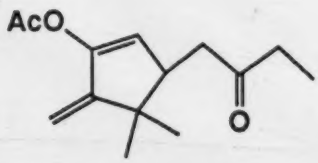


107

Anhydrous potassium carbonate (0.10 g) was added to a solution of diketone **103** (1.26 g, 6.49 mmol) in methanol (8 mL). After stirring at room temperature for 6 h, the mixture was poured into water (50 mL) and extracted with methylene chloride (3 x 30 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (1:5) afforded the starting material **103** (0.30 g, 24% recovery). Further elution with ether-hexane (3:7) gave diketone **107** (0.381 g, 1.69 mmol, 26% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 0.75 (s, 3H, $-CH_3$), 1.07 (t, 3H,

J = 7.5 Hz, -CH_2CH_3), 1.21 (s, 3H, -CH_3), 1.70 (dd, 1H, J = 19, 11 Hz), 2.06 (m, 1H, C-4 CH), 2.34 (dd, 1H, J = 13, 6 Hz), 2.32 (m, 1H, C-2 CH), 2.48 (q, 2H, J = 7.5 Hz, -CH_2CH_3), 2.55 (dd, 1H, J = 19, 5 Hz), 2.64 (d, 1H, J = 13 Hz), 3.34 (s, 3H, -OCH_3), 3.42 (dd, 1H, J = 10, 8 Hz, -CH_2O-), and 3.66 (dd, 1H, J = 10, 5 Hz, -CH_2O-); ir 1739 (C=O) and 1714 cm^{-1} (C=O); ms M^+ 226.1570 (calcd. for $C_{13}H_{22}O_3$: 226.1569). Further elution with ether-hexane (4:6) gave rise to keto alcohol **106** (0.617 g, 3.19 mmol, 49% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 1.00 (s, 3H, -CH_3), 1.10 (d, 3H, J = 7.5 Hz, -$CHCH_3$), 1.20 (s, 3H, -CH_3), 1.82 (s, 1H, -OH), 2.0-2.6 (complex, 5H), 2.75 (q, 1H, J = 7.5 Hz, -$CHCH_3$), 5.04 and 5.07 (s, 1H each, =CH_2); ir 3445 (OH), 1702 (C=O), and 1655 cm^{-1} (C=C); ms M^+ 194.1305 (calcd. for $C_{12}H_{18}O_2$: 194.1307).

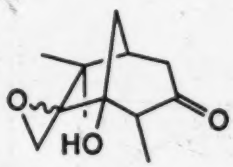
1-Acetoxy-4,4-dimethyl-5-methylidene-3-(2-oxobutyl)-cyclopentene (108)



To a solution of diketone **103** (54 mg, 0.278 mmol) in methylene chloride (10 mL), were added acetic anhydride (121 mg, 1.19 mmol), pyridine (100 mg, 1.26 mmol) and DMAP (65 mg, 0.316 mmol). After stirring at room temperature for 48 h, the reaction mixture was poured into 1 *N* aqueous hydrochloric acid and extracted with methylene chloride (2 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. Purification of the crude product by flash

concentrated. Purification of the crude product by flash chromatography gave rise to acetate **108** (31 mg, 0.131 mmol, 47% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (s, 3H, -CH_3), 1.00 (t, 3H, J = 7.5 Hz, -CH_2CH_3), 1.15 (s, 3H, -CH_3), 2.15 (s, 3H, -$COCH_3$), 2.1-3.1 (complex, 5H), 4.65, 4.85, and 5.75 (s, 1H each, vinylic **H**); ms M^+ 236.1413 (calcd. for $C_{14}H_{20}O_3$: 236.1412).

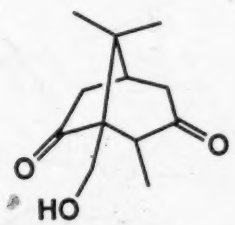
Spiro(1-hydroxy-2,6,6-trimethylbicyclo[3.2.1]octan-3-one)-7,2'-oxirane (109)



MCPBA (70% pure, 865 mg, 3.51 mmol) was added to a solution of **106** (623 mg, 3.21 mmol) in methylene chloride (10 mL). After stirring at room temperature for 6 h, calcium hydroxide powder (430 mg, 5.8 mmol) was added. The mixture was allowed to stir for 10 min and filtered. The residue was washed with methylene chloride (20 mL). The filtrate was washed with 1 *N* aqueous sodium hydroxide solution (10 mL) and brine (10 mL). The organic layer was dried, filtered and concentrated. The residue was chromatographed on silica gel. Elution with a solution of 35% ether in hexane afforded a mixture of two epimeric epoxy alcohols **109** (573 mg, 2.73 mmol, 85% yield). Further elution with 40% ether in hexane gave diketo alcohol **95** (67 mg, 0.321 mmol, 10% yield). The mixture was partially separated by flash chromatography to give *endo*-**109** (minor): ^{1}H nmr (200 MHz, $CDCl_3$)

109 (minor): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.91 (s, 3H, -CH_3), 1.02 (s, 3H, -CH_3), and 1.27 (d, 3H, J = 7.5 Hz, -CH(CH_3)-); and *exo*-**109** (major): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.89 (s, 3H, -CH_3), 0.96 (s, 3H, -CH_3), 1.10 (d, 3H, J = 7.5 Hz, -CH(CH_3)-), 2.06 (d, 1H, J = 12 Hz, C-8 CH_2), 2.07-2.38 (complex, 3H), 2.44 (dd, 1H, J = 12, 5 Hz, C-8 CH_2), 2.68 (bs, 1H, OH), 2.80 (q, 1H, J = 7.5 Hz, -CH(CH_3)-), 2.82 (d, 1H, J = 4 Hz, C-3' CH_2), and 2.94 (d, 1H, J = 4 Hz, C-3' CH_2); ir 3499 (OH) and 1707 cm^{-1} (C=O); ms M^+ 210.1257 (calcd. for $C_{12}H_{18}O_3$: 210.1256); Anal. Calcd. for $C_{12}H_{18}O_3$: C 68.54, H 8.63; Found: C 68.29, H 8.65.

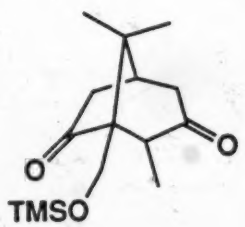
4,8,8-trimethyl-5-hydroxymethylbicyclo[3.2.1]octane-3,6-dione (95)



Stannic chloride (0.36 mL, 3.27 mmol) was added to a solution of epoxy alcohols **109** (573 mg, 2.73 mmol) in chloroform (15 mL). After stirring at room temperature for 10 h, water (20 mL) was added. The resulting mixture was poured into 1 *N* aqueous hydrochloric acid (50 mL) and extracted with methylene chloride (3 x 30 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (4:6) gave diketo alcohol **95** (533 mg, 2.53 mmol, 93% yield): mp 96-

diketo alcohol **95** (533 mg, 2.53 mmol, 93% yield): mp 96-97°C; ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J* = 7 Hz, -CH(CH_3)-), 1.16 (s, 3H, -CH_3), 1.42 (s, 3H, -CH_3), 1.65 (bs, 1H, -OH), 1.98 (d, 1H, *J* = 19 Hz, C-7 CH_2), 2.22 (ddd, 1H, *J* = 7, 4, 3 Hz, C-1 CH), 2.39 (dd, 1H, *J* = 17, 3 Hz, C-2 CH_2), 2.60 (ddd, 1H, *J* = 19, 7, 2 Hz, C-7 CH_2), 2.90 (ddd, 1H, *J* = 17, 4, 2 Hz, C-2 CH_2), 3.03 (q, 1H, *J* = 7 Hz, -CH(CH_3)-), 3.75 (d, 1H, *J* = 12 Hz, -CHHOH), and 3.92 (d, 1H, *J* = 12 Hz, -CHHOH); ir 3485 (OH), 1733 (C=O), and 1704 cm^{-1} (C=O); ms M^+ 210.1257 (calcd. for $C_{12}H_{18}O_3$: 210.1256); Anal. Calcd. for $C_{12}H_{18}O_3$: C 68.54, H 8.63; Found: C 68.75, H 8.82.

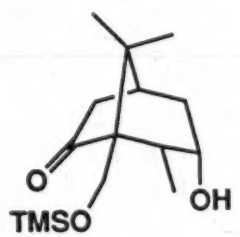
4,8,8-Trimethyl-5-trimethylsiloxymethylbicyclo[3.2.1]octane-3,6-dione (110)



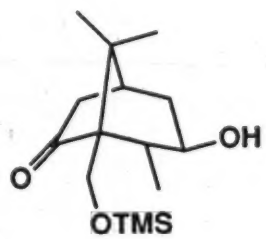
To a solution of diketo alcohol **95** (1.32 g, 6.29 mmol) in methylene chloride (50 mL), were added DMAP (77 mg, 0.63 mmol) and triethylamine (1.92 mL, 13.8 mmol). The resulting solution was cooled to 0°C and trimethylsilyl chloride (1.60 mL, 12.58 mmol) was added. After stirring at room temperature for 7 h, the reaction mixture was poured into ice-cold 1 *N* aqueous hydrochloric acid and extracted with methylene chloride (3 x 20 mL). The extracts were washed with water, dried, filtered

and concentrated. Purification of the crude material by flash chromatography gave **95** (92 mg, 7% recovery) and diketo silyl ether **110** (1437 mg, 5.09 mmol, 81% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.12 (s, 9H, -Si(CH_3)$_3$), 1.04 (d, 3H, J = 7 Hz, -CH(CH_3)-), 1.12 (s, 3H, -CH_3), 1.40 (s, 3H, -CH_3), 2.00 (d, 1H, J = 19 Hz, C-7 CH_2), 2.23 (ddd, 1H, J = 7.5, 4, 2 Hz, C-1 CH), 2.41 (dd, 1H, J = 17, 2 Hz, C-2 CH_2), 2.60 (ddd, 1H, J = 19, 7.5, 2 Hz, C-7 CH_2), 2.92 (ddd, 1H, J = 17, 4, 2 Hz, C-2 CH_2), 3.12 (q, 1H, J = 7 Hz, -CH(CH_3)-), 3.64 (d, 1H, J = 11 Hz, -CHHO-), and 3.88 (d, 1H, J = 11 Hz, -CHHO-); ir 1736 (C=O) and 1710 cm^{-1} (C=O); ms M$^+$ 282.1653 (calcd. for $C_{15}H_{26}O_3Si$: 282.1651).

3-Hydroxy-4,8,8-trimethyl-5-trimethylsiloxymethylbicyclo-[3.2.1]octan-6-ones (111a and 111b)



111a

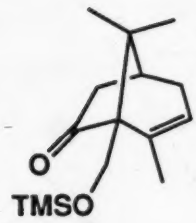


111b

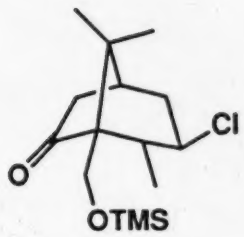
Under an argon atmosphere, a solution of diketo silyl ether **110** (1.45 g, 5.142 mmol) in ether (40 mL) and tetrahydrofuran (20 mL) was cooled to -30°C and lithium tri-*tert*-butoxyaluminum hydride (95% purity, 1.76 g, 6.58 mmol) was added. After stirring at the same temperature for 35 h, water (5 mL) was added. The resulting mixture was poured into 1 *N*

aqueous hydrochloric acid (60 mL) and extracted with ether (3 x 50 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (4:6) gave alcohol **111a** (1.38 g, 4.859 mmol, 94% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.09 (s, 9H, -Si(CH_3)$_3$), 1.00 (s, 3H, -CH_3), 1.02 (d, 2H, J = 7 Hz, -CH(CH_3)-), 1.23 (s, 3H, -CH_3), 1.53 (bs, 1H, OH), 1.83 (dd, 1H, J = 14, 3.5 Hz, C-2 CH_2), 1.92 (ddd, 1H, J = 7, 3.5, 3.5 Hz, C-1 CH), 2.30 (ddd, 1H, J = 14, 3.5, 2 Hz, C-2 CH_2), 2.36 (ddd, 1H, J = 19, 7, 2 Hz, C-7 CH_2), 2.65 (qd, 1H, J = 7, 5 Hz, -CH(CH_3)-), 2.67 (d, 1H, J = 19 Hz, C-7 CH_2), 3.54 (d, 1H, J = 11 Hz, -CHHO-), 3.88 (d, 1H, J = 11 Hz, -CHHO-), and 4.01 (dd, 1H, J = 5, 4.5 Hz, -CH(OH)-); ir 3500 (OH) and 1730 cm^{-1} (C=O); ms M$^+$ 284.1804 (calcd. for $C_{15}H_{28}O_3Si$: 284.1808). Further elution with ether-hexane (4.5:5.5) afforded **111b** (73 mg, 0.257 mmol, 5% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.09 (s, 9H, -Si(CH_3)$_3$), 0.97 (s, 3H, -CH_3), 0.98 (d, 3H, J = 7 Hz, -CH(CH_3)-), 1.28 (s, 3H, -CH_3), 1.54 (s, 1H, -OH), 1.95 (d, 1H, J = 19 Hz, C-7 CH_2), 1.98 (complex, 3H), 2.30 (m, 1H, C-1 CH), 2.42 (dd, 1H, J = 19, 7 Hz, C-7 CH_2), 3.40 (m, 1H, -CH(OH)-), 3.50, and 3.87 (both d, 1H each, J = 11 Hz each, -CH_2O-); ir 3280 (OH) and 1727 cm^{-1} (C=O); ms M$^+$ 284.1806 (calcd. for $C_{15}H_{28}O_3Si$: 284.1808).

4,8,8-Trimethyl-5-trimethylsiloxymethylbicyclo[3.2.1]oct-3-en-6-one (112) and 3-chloro-4,8,8-trimethyl-5-trimethylsiloxymethylbicyclo[3.2.1]octan-6-one (113)



112

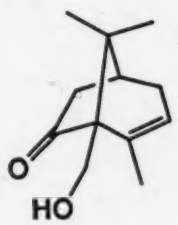


113

A solution of keto alcohol **111a** (196 mg, 0.69 mmol) in methylene chloride (10 mL) was cooled to 0°C under an argon atmosphere and thionyl chloride (0.10 mL) and pyridine (0.22 mL) were added. After stirring at room temperature for 24 h, the reaction solution was poured into ice-cold 1 *N* aqueous hydrochloric acid and extracted with methylene chloride (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (1:50) gave enone **112** (160 mg, 0.602 mmol, 87% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.15 (s, 9H, -Si(CH_3)$_3$), 1.00 (s, 3H, -CH_3), 1.14 (s, 3H, -CH_3), 1.80 (bs, 3H, vinylic CH_3), 1.81 (m, 1H, C-1 C**H**), 1.88 (d, 1H, *J* = 14 Hz, C-2 CH_2), 2.08 (d, 1H, *J* = 18 Hz, C-7 CH_2), 2.52 (dd, 1H, *J* = 18, 7 Hz, C-7 CH_2), 2.52 (d, 1H, *J* = 14 Hz, C-2 CH_2), 3.74 (d, 1H, *J* = 10 Hz, -OCH_2-), 4.10 (d, 1H, *J* = 10 Hz, -OCH_2-), and 5.5 (bs, 1H, =C**H**-); ir 1731 cm^{-1} (C=O); ms M^+ 266.1698 (calcd. for $C_{15}H_{26}O_2Si$: 266.1702). Further elution with ether-hexane (1:25) afforded by-product **113** (23 mg, 0.076 mmol, 11% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.10 (s, 9H, -Si(CH_3)$_3$), 0.99 (s, 3H, -CH_3), 1.06 (d, 3H, *J* = 6.5 Hz, -CHCH_3), 1.32 (s, 3H, -CH_3), 1.96 (d, 1H,

J = 19 Hz, C-7 CH_2), 2.00 (dd, 1H, J = 8, 4.5 Hz, C-1 CH), 2.15 (ddd, 1H, J = 14, 7, 4.5 Hz, C-2 CH_2), 2.40 (dd, 1H, J = 14, 11 Hz, C-2 CH_2), 2.44 (dd, 1H, J = 19, 8 Hz, C-7 CH_2), 2.58 (dq, 1H, J = 11, 6.5 Hz, -$CHCH_3$), 3.49(d, 1H, J = 11 Hz, -OCH_2-), 3.65 (ddd, 1H, J = 11, 11, 7 Hz, -CHCl-), and 3.88 (d, 1H, J = 11 Hz, -OCH_2-); ms M^+ 302.1469 and 304.1451 (calcd. for $C_{15}H_{27}ClO_2Si$: 302.1469 and 304.1449).

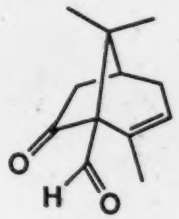
5-Hydroxymethyl-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (115)



To a solution of compound **112** (218 mg, 0.82 mmol) in tetrahydrofuran (3 mL), was added 1*M* tetrabutylammonium fluoride solution in tetrahydrofuran (1.5 mL). After stirring at room temperature for 24 h, the reaction mixture was poured into water (50 mL) and extracted with ether (3 x 10 mL). The extracts were combined, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with ether-hexane (3:7) afforded enone alcohol **115** (147 mg, 0.578 mmol, 92% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.05 (s, 3H, -CH_3), 1.10 (s, 3H, -CH_3), 1.80 (bs, 1H, -OH), 1.82 (bs, 3H, vinylic CH_3), 1.84 (m, 1H, C-1 CH), 1.92 (dd, 1H, J = 16, 4 Hz, C-2 CH_2), 2.10 (d, 1H, J = 18 Hz, C-7 CH_2), 2.48 (dd, 1H, J = 16, 5 Hz, C-2 CH_2), 2.52 (dd,

1H, J = 18, 7.5 Hz, C-7 CH_2), 3.92 (d, 1H, J = 12 Hz, -CH_2OH), 4.12 (d, 1H, J = 12 Hz, -CH_2OH), and 5.60 (bs, 1H, =CH-); ir 3480 (OH) and 1728 cm^{-1} (C=O); ms M^+ 194.1311 (calcd. for $C_{12}H_{18}O_2$: 194.1307).

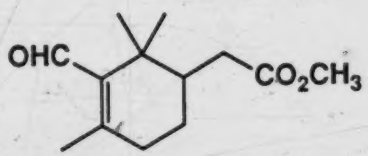
5-Formyl-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (99)



Under an argon atmosphere, a solution of oxalyl chloride (0.028 mL, 0.33 mmol) in methylene chloride (3 mL) was cooled to -78°C and a solution of DMSO (0.042 mL, 0.59 mmol) in methylene chloride (2 mL) was added dropwise over a period of 3 min. After stirring for 20 min, a solution of alcohol **115** (53 mg 0.27 mmol) in methylene chloride (2 mL) was added slowly. After stirring for another 20 min, a solution of triethylamine (0.0927 mL, 0.66 mmol) in methylene chloride (2 mL) was introduced. The mixture was allowed to warm up slowly to room temperature. The resulting mixture was poured into ice-cold 1 *N* aqueous hydrochloric acid (20 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (1:4) afforded aldehyde **99** (42 mg, 0.219 mmol, 81% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.05 (s, 3H, -CH_3), 1.12, (s, 3H, -CH_3), 1.69 (bs,, 3H, vinylic CH_3), 1.90 (m, 1H, C-1 CH), 1.98 (d, 1H, J = 18 Hz, C-2 CH_2), 2.18 (d, 1H, J = 19 Hz, C-7 CH_2), 2.54 (d,

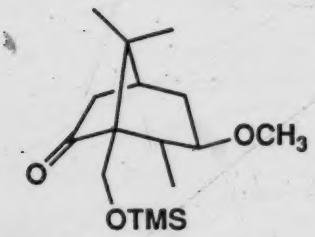
2.18 (d, 1H, J = 19 Hz, C-7 CH_2), 2.54 (d, 1H, J = 18 Hz, C-2 CH_2), 2.72 (dd, 1H, J = 19, 7 Hz, C-7 CH_2), 5.55 (bs, 1H, =CH-), and 9.95 (s, 1H, -CHO); ir 1735 (ketone C=O) and 1717 cm^{-1} (aldehyde C=O); ms M^+ 192.1148 (calcd. for $C_{12}H_{16}O_2$: 192.1150).

2-Formyl-4-methoxycarbonylmethyl-1,3,3-trimethylcyclohexene (116)



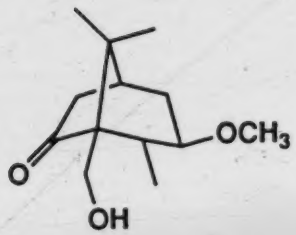
To a solution of aldehyde **99** (38 mg, 0.196 mmol) in methanol (3 mL), were added potassium carbonate (5 mg) and 1-nitropropane (0.023 mL, 0.255 mmol). After stirring at room temperature for 12 h, the mixture was poured into water and extracted with methylene chloride (3 x 15 mL). The extracts were dried, filtered and concentrated. The crude product was purified by flash chromatography to give **116** (30 mg, 0.134 mmol, 68% yield): ^1H nmr (80 MHz, $CDCl_3$) δ 0.90 (s, 3H, $-CH_3$), 1.12 (s, 3H, $-CH_3$), 1.95 (s, 3H, vinylic CH_3), 1.2-2.8 (complex, 7H),. 3.55 (s, 3H, $-OCH_3$), and 10.00 (s, 1H, -CHO); ir 1737 (ester C=O) and 1671 cm^{-1} (aldehyde C=O); ms M^+ 224.1410 (calcd. for $C_{13}H_{20}O_3$: 224.1412).

3-Methoxy-4,8,8-trimethyl-5-trimethylsiloxymethylbicyclo[3.2.1]octan-6-one (117)



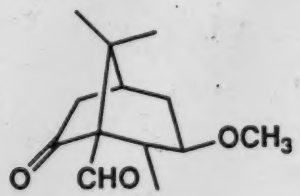
To a solution of alcohol **111b** (67 mg, 0.236 mmol) in tetrahydrofuran (10 mL), were added sodium hydride (14 mg) and iodomethane (0.029 mL). After stirring at room temperature for 10 h, the mixture was poured into water (50 mL) and extracted with methylene chloride (2 x 20 mL). The extracts were combined, dried, filtered and concentrated. The crude product was purified by flash chromatography to give methyl ether **117** (60 mg, 0.203 mmol, 86% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.08 (s, 9H, -Si(CH_3)$_3$), 0.93 (d, 3H, J = 6 Hz, -CH(CH_3)-), 0.96 (s, 3H, -CH_3), 1.23 (s, 3H, -CH_3), 1.82 (dddd, 1H, J = 13, 10, 3, 1 Hz, C-2 CH_2), 1.92 (d, 1H, J = 19 Hz, C-7 CH_2), 1.97 (m, 1H, C-1 CH), 2.03 (ddd, 1H, J = 13, 7, 4 Hz, C-2 CH_2), 2.34 (dq, 1H, J = 11, 6 Hz, -CH(CH_3)-), 2.42 (ddd, 1H, J = 19, 7, 1 Hz, C-7 CH_2), 2.88 (ddd, 1H, J = 11, 10, 7 Hz, -CH(OCH_3)-), 3.33 (s, 3H, -OCH_3), 3.50 (d, 1H, J = 11 Hz, -CH_2O-), and 3.84 (d, 1H, J = 11 Hz, -CH_2O-); ir 1734 cm^{-1} (C=O); ms M^+ 298.1965 (calcd. for $C_{16}H_{30}O_3Si$: 298.1964).

5-Hydroxymethyl-3-methoxy-4,8,8-trimethylbicyclo[3.2.1]-octan-6-one (118)



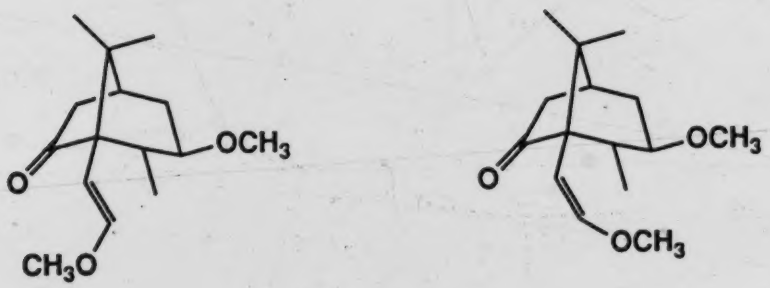
Potassium fluoride (0.5 g) and silyl ether **117** (60 mg, 0.203 mmol) were placed in a mixture of water and methanol (1:5, 5 mL). The mixture was heated under reflux for 4 h, then poured into water (30 mL) and extracted with methylene chloride (3 x 15 mL). The extracts were dried, filtered and concentrated, giving alcohol **118** (44 mg, 0.199 mmol, 98% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.02 (d, 3H, J = 7 Hz, -CH(CH_3)-), 1.05 (s, 3H, -CH_3), 1.28 (s, 3H, -CH_3), 1.59 (bs, 1H, -OH), 1.81 (ddd, 1H, J = 14, 10, 4 Hz, C-2 CH_2), 1.98 (d, 1H, J = 19 Hz, C-7 CH_2), 2.04 (m, 1H, C-1 CH), 2.07 (ddd, 1H, J = 14, 6.5, 3.5 Hz, C-2 CH_2), 2.26 (dq, 1H, J = 10.5, 7 Hz, -CH(CH_3)-), 2.48 (dd, 1H, J = 19, 8 Hz, C-7 CH_2), 2.90 (ddd, 1H, J = 10, 10, 6.5 Hz, -CH(OCH_3)-), 3.34 (s, 3H, -OCH_3), 3.67 (d, 1H, J = 12 Hz, -CH_2O-), and 3.94 (d, 1H, J = 12 Hz, -CH_2O-).

5-Formyl-3-methoxy-4,8,8-trimethylbicyclo[3.2.1]octan-6-one (119)



In a similar procedure to the one for compound **99** using oxalyl chloride (0.018 mL), DMSO (0.027 mL) and triethylamine (0.060 mL), oxidation of alcohol **118** (40 mg, 0.177 mmol) gave aldehyde **119** (36 mg, 0.159 mmol, 90% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.96 (d, 3H, *J* = 6.5 Hz, -CH(CH_3)-), 1.04 (s, 3H, -CH_3), 1.26 (s, 3H, -CH_3), 1.87 (ddd, 1H, *J* = 14, 10, 4 Hz, C-2 CH_2), 2.08 (ddd, 1H, *J* = 14, 6.5, 3.5 Hz, C-2 CH_2), 2.10 (m, 1H, C-1 CH), 2.12 (d, 1H, *J* = 19 Hz, C-7 CH_2), 2.41 (dq, 1H, *J* = 10, 6.5 Hz, -CH(CH_3)-), 2.68 (dd, 1H, *J* = 19, 7 Hz, C-7 CH_2), 2.97 (ddd, 1H, *J* = 10, 10, 6.5 Hz, -CH(OCH_3)-), 3.32 (s, 3H, -OCH_3), and 9.80 (s, 1H, -CHO).

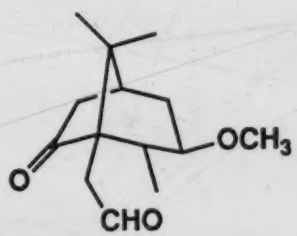
3-Methoxy-5-(2-methoxyvinyl)-4,8,8-trimethyl-bicyclo[3.2.1]octan-6-ones (120)



Under an argon atmosphere, a 1.4 *M* butyllithium solution (0.4 mL, 0.56 mmol) was added to a mixture of methoxymethyltriphenylphosphonium chloride (200 mg, 0.584 mmol) and benzene (10 mL). After the mixture had been stirred for 5 min, a solution of aldehyde **119** (40 mg, 0.178 mmol) in benzene (2 mL) was added dropwise. After stirring at room

temperature for 18 h, the mixture was poured into water (50 mL) and extracted with ether (3 x 15 mL). The extracts were dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (3:7) gave a mixture of *cis* and *trans*-**120** (35 mg, 0.139 mmol, 78% yield). The isomers were partially isolated by flash chromatography. *cis*-**120**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.86 (s, 3H, -CH_3), 0.91 (d, 3H, J = 6 Hz, -CH(CH_3)-), 1.16 (s, 3H, -CH_3), 1.7-3.0 (complex, 7H), 3.32 (s, 3H, -OCH_3), 3.49 (s, 3H, =CHOCH_3), 4.00 (d, 1H, J = 7.5 Hz, -CH=), and 5.92 (d, 1H, J = 7.5 Hz, =CHOCH_3). *trans*-**120**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.82 (s, 3H, -CH_3), 0.93 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.10 (s, 3H, -CH_3), 1.7-3.0 (complex, 7H), 3.31 (s, 3H, -OCH_3), 3.53 (s, 3H, =CHOCH_3), 4.36 (d, 1H, J = 13 Hz, -CH=), and 6.47 (d, 1H, J = 13 Hz, =CHOCH_3).

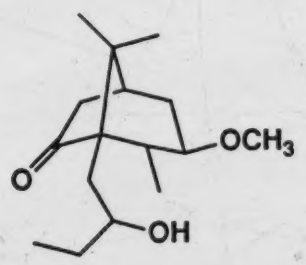
3-Methoxy-4,8,8-trimethyl-5-(2-oxoethyl)bicyclo[3.2.1]octan-6-one (121)



To a solution of the epimeric mixture of **120** (29 mg, 0.115 mmol) in ether (1 mL), was added 35% aqueous perchloric acid (1 mL). After stirring at room temperature for 30 min, the mixture was poured into an aqueous sodium bicarbonate solution (40 mL) and extracted with methylene

chloride (3 x 15 mL). The extracts were washed with water, dried, filtered and concentrated, giving aldehyde **121** (25 mg, 0.105 mmol, 91% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (s, 3H, -CH_3), 1.02 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.19 (s, 3H, -CH_3), 1.84 (dddd, 1H, J = 11, 10, 1.5, 1.5 Hz, C-2 CH_2), 2.06 (d, 1H, J = 19 Hz, C-7 CH_2), 2.10 (m, 1H, C-1 CH), 2.11 (dd, 1H, J = 11, 6.5 Hz, C-2 CH_2), 2.25 (d, 1H, J = 16, 4 Hz, -CH_2CHO), 2.31 (dq, 1H, J = 10, 6.5 Hz, -CH(CH_3)-), 2.50 (dd, 1H, J = 19, 8 Hz, C-7 CH_2), 2.84(dd, 1H, J = 16, 2 Hz, -CH_2CHO), 2.89 (ddd, H, J = 10, 10, 6.5 Hz, -CH(OCH_3)-), 3.35 (s, 3H, -OCH_3), and 9.90 (dd, 1H, J = 4, 2 Hz, -CHO).

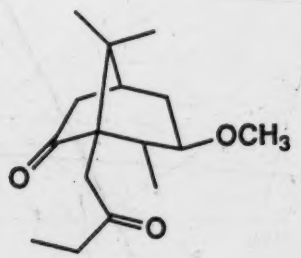
5-(2-Hydroxybutyl)-3-methoxy-4,8,8-trimethylbicyclo[3.2.1]-octan-6-one (122)



To a solution of compound **121** (20 mg, 0.084 mmol) in tetrahydrofuran (2 mL), was added a 1*M* solution of ethylmagnesium bromide (0.2 mL, 0.20 mmol). After stirring at room temperature for 2.5 h, the mixture was poured into water (20 mL) and extracted with methylene chloride. The extracts were dried, filtered and concentrated. The crude product was subjected to flash chromatography. Elution with ether-hexane (3:7) gave rise to keto alcohol **122** (20 mg, 0.075 mmol, 89% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz, -CH_2CH_3),

MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz, -CH_2CH_3), 0.98 (s, 3H, -CH_3), 1.02 (d, 3H, J = 7 Hz, -CH(CH_3)-), 1.26 (s, 3H, -CH_3), 1.36 (d, 1H, J = 3 Hz, -OH), 1.49 (dq, 2H, J = 7.5, 7.5 Hz, -CH_2CH_3), 2.04 (d, 1H, J = 20 Hz, C-7 CH_2), 1.7-2.2 (complex, 5H), 2.33 (dq, 1H, J = 10, 7 Hz, -CH(CH_3)-), 2.50 (dd, 1H, J = 20, 7.5 Hz, C-7 CH_2), 2.86 (ddd, 1H, J = 10, 10, 6.5 Hz, -CH(OCH_3)-), 3.35 (s, 3H, -OCH_3), and 4.02 (m, 1H, -CHOH-).

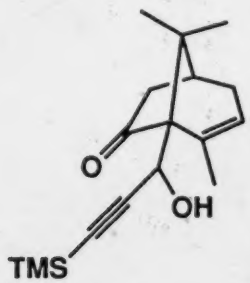
3-Methoxy-4,8,8-trimethyl-5-(2-oxobutyl)bicyclo[3.2.1]octan-6-one (123)



In a similar procedure to the one for compound **99** using oxalyl chloride (0.010 mL), DMSO (0.014 mL) and triethylamine (0.030 mL), oxidation of alcohol **122** (20 mg, 0.075 mmol) gave diketone **123** (17 mg, 0.064 mmol, 85% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 0.85 (d, 3H, J = 6 Hz, -CH(CH_3)-), 0.91 (s, 3H, -CH_3), 1.06 (t, 3H, J = 7.5 Hz, -CH_2CH_3), 1.24 (s, 3H, -CH_3), 2.01 (d, 1H, J = 19 Hz, C-7 CH_2), 1.8-2.2 (complex, 3H), 2.30 (d, 1H, J = 18 Hz, C-1' CH_2), 2.46 (ddd, 1H, J = 19, 7, 1.5 Hz, C-7 CH_2), 2.48 (q, 2H, J = 7.5 Hz, -CH_2CH_3), 2.75 (dq, 1H, J = 11, 6 Hz, -CH(CH_3)-), 2.85 (ddd, 1H, J = 11, 11, 6 Hz, -CH(OCH_3)-), 2.98 (d, 1H, J = 18 Hz, C-1' CH_2), and 3.40 (s, 3H,

J = 18 Hz, C-1' CH_2), and 3.40 (s, 3H, -OCH_3); ir 1732 (C=O) and 1709 cm^{-1} (C=O); ms M^+ 266.1879 (calcd. for $C_{16}H_{26}O_3$: 266.1882).

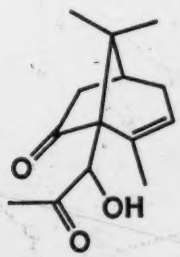
5-(1-Hydroxy-3-trimethylsilyl-2-propynyl)-4,8,8-trimethyl-bicyclo[3.2.1]oct-3-en-6-ones (124a and 124b)



Under an argon atmosphere, a solution of trimethylsilylacetylene (0.15 mL, 1.04 mmol) in tetrahydrofuran was cooled to -78°C and a 1.0 *M* butyllithium solution (0.60 mL, 0.6 mmol) was added. After stirring for 10 min, a solution of aldehyde **99** (100 mg, 0.521 mmol) in tetrahydrofuran (2 mL) was added dropwise. After stirring at -78°C for 4.5 h, the reaction mixture was poured into aqueous ammonium chloride solution (20 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were combined, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (1:4) gave **124a** (35 mg, 0.121 mmol, 23% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 0.18 (s, 9H, -$Si(CH_3)_3$), 1.08 (s, 3H, -CH_3), 1.18 (s, 3H, -CH_3), 1.80 (m, 1H, C-1 CH), 1.90 (d, 1H, J = 18 Hz, C-2 CH), 2.10 (bs, 3H, vinylic CH_3), 2.16 (d, 1H, J = 19 Hz, C-7 CH_2), 2.50 (d, 1H, J = 18 Hz, C-2 CH_2), 2.62 (dd, 1H, J = 19, 7.5 Hz, C-7 CH_2), 4.93 (s, 1H, D_2O exchangeable, -OH), 5.00 (s, 1H, -CHOH-), and

1H, -CHOH-), and 5.62 (bs, 1H, =CH-). Further elution with ether-hexane (1:3) afforded another epimer **124b** (103 mg, 0.355 mmol, 68% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.20 (s, 9H, -Si(CH_3)$_3$), 1.24 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3), 1.78 (m, 1H, C-1 CH), 1.80 (bs, 3H, vinylic CH_3), 1.88 (d, 1H, J = 19 Hz, C-2 CH_2), 2.09 (d, 1H, J = 18 Hz, C-7 CH_2), 2.36 (d, 1H, J = 4.5 Hz, D_2O exchangeable, -OH), 2.52 (d, 1H, J = 19 Hz, C-2 CH_2), 2.60 (dd, 1H, J = 18, 7 Hz, C-7 CH_2), 5.28 (d, 1H, J = 4.5 Hz, -CHOH-), and 5.60 (bs, 1H, =CH-); ir 3485 (OH), 2175 (C≡C), and 1728 cm^{-1} (C=O); ms M^+ 290.1703 (calcd. for $C_{17}H_{26}O_2Si$: 290.1702).

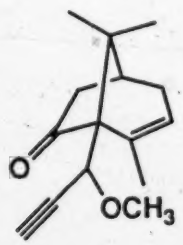
5-(1-Hydroxy-2-oxopropyl)-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (125)



To a solution of compound **124b** (90 mg, 0.31 mmol) in methanol (10 mL), was added potassium fluoride (100 mg). After stirring at room temperature for 4.5 h, mercury(II) chloride (270 mg) and 20% aqueous sulfuric acid (1.0 mL) were added. After stirring for additional 18 h, the reaction mixture was poured into 1 *N* aqueous hydrochloric acid (30 mL) and extracted with methylene chloride (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (3:7)

afforded α-hydroxy ketone **125** (67 mg, 0.284 mmol, 91% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.92 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 1.73 (m, 1H, C-1 C**H**), 1.87 (d, 1H, *J* = 19 Hz, C-2 CH_2), 1.87 (bs, 3H, vinylic CH_3), 2.10 (d, 1H, *J* = 19 Hz, C-7 CH_2), 2.34 (s, 3H, -$COCH_3$), 2.50 (d, H, *J* = 19 Hz, C-2 CH_2), 2.62 (dd, 1H, *J* = 19, 8 Hz, C-7 CH_2), 3.24 (d, 1H, *J* = 4 Hz, -CHO**H**-), 4.98 (d, 1H, *J* = 4 Hz, -C**H**OH-), and 5.67 (bs, 1H, =C**H**-); ir 3408 (OH) and 1709 cm^{-1} (C=O); ms M^+ 236.1416 (calcd. for $C_{14}H_{20}O_3$: 236.1412).

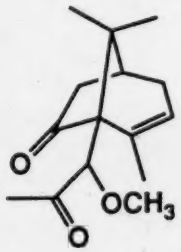
5-(1-Methoxy-2-propynyl)-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (126)



To a solution of compound **124a** (30 mg, 0.104 mmol) in dimethoxyethane (3 mL), was added sodium hydride (50% pure, 6 mg, 0.12 mmol). After stirring at room temperature for 10 min, iodomethane (0.010 mL, 0.16 mmol) was added. After stirring for an additional period of 2.5 h, the reaction mixture was poured into ice-cold water (20 mL) and extracted with methylene chloride (2 x 10 mL). The extracts were combined, dried, filtered and concentrated, giving compound **126** (23 mg, 0.10 mmol, 95% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.15 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.72 (bs, 3H, vinylic CH_3), 1.88 (m, 1H, C-1

CH), 1.90 (d, 1H, J = 14 Hz, C-2 CH_2), 2.10 (d, 1H, J = 18 Hz, C-7 CH_2), 2.50 (d, 1H, J = 14 Hz, C-2 CH_2), 2.60 (d, 1H, J = 2 Hz, -C≡CH), 2.75 (dd, 1H, J = 18, 7.5 Hz, C-7 CH_2), 3.48 (s, 3H, -OCH_3), 4.75 (d, 1H, J = 2 Hz, -$CHOCH_3$-), and 5.52 (bs, 1H, =CH-).

5-(1-methoxy-2-oxopropyl)-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (127)



To a solution of compound **126** (23 mg, 0.10 mmol) in methanol (5 mL), were added mercury(II) chloride (10 mg), and 20% sulfuric acid (1mL). After stirring at room temperature for 7 h, the mixture was poured into water and extracted with methylene chloride (3 x 10 mL). The extracts were washed with brine, dried, filtered and concentrated. The residue was purified by flash chromatography. Elution with ether-hexane (3:7) gave methyl ketone **127** (14 mg, 0.056 mmol, 56% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.92 (s, 3H, -CH_3), 1.13 (s, 3H, -CH_3), 1.73 (m, 1H, C-1 CH), 1.78 (bs, 3H, vinylic CH_3), 1.86 (d, 1H, J = 19 Hz, C-2 CH_2), 2.16 (d, 1H, J = 18 Hz, C-7 CH_2), 2.27 (s, 3H, -$COCH_3$), 2.50 (d, 1H, J = 19 Hz, C-2 CH_2), 2.67 (dd, 1H, J = 18, 7.5 Hz, C-7 CH_2), 3.33 (s, 3H, -OCH_3), 4.33 (s, 1H, -CH(OCH_3)-), and 5.63 (bs, 1H, =CH-).

Cyclization experiments of compounds 123 and 127

A. With potassium carbonate

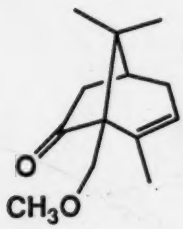
Potassium carbonate (20 mg) was added to a solution of **127** (14 mg, 0.056 mmol) in acetone (3 mL). After stirring at room temperature for 12 h, the mixture was poured into brine (20 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were dried, filtered and concentrated. Flash chromatography of the residue gave only recovered starting diketone **127** (12 mg).

Potassium carbonate (20 mg) was added to a solution of compound **123** (15 mg, 0.055 mmol) in methanol (3 mL). After stirring at room temperature for 10 h, the mixture was poured into brine (20 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were dried, filtered and concentrated. Flash chromatography of the residue gave only recovered starting diketone **123** (10 mg).

B. With *p*-toluenesulfonic acid in refluxing benzene

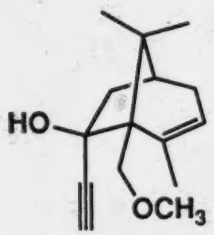
A solution of compound **127** (12 mg, 0.048 mmol) and *p*-toluenesulfonic acid (100 mg) in benzene (30 mL) was heated under reflux for 8 h. Then the reaction solution was washed with 1 *N* aqueous sodium hydroxide solution (20 mL) and water (30 mL). The organic layer was dried, filtered and concentrated. The purification of the residue by flash chromatography gave no identified compound. When the same reaction conditions were applied to compound **123** (10 mg), no desired product was obtained.

5-Methoxymethyl-4,8,8-trimethylbicyclo[3.2.1]oct-3-en-6-one (128)

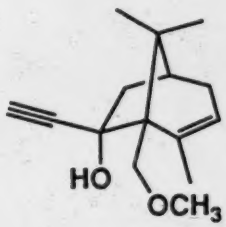


To a solution of enone alcohol **115** (177 mg, 0.91 mmol) in dimethoxyethane (5 mL), was added sodium hydride (50% pure, 88 mg, 1.82 mmol). After stirring at room temperature for 20 min, iodomethane (0.074 mL, 1.18 mmol) was added. After stirring for 12 h, the reaction mixture was poured into water (30 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were combined, dried, filtered and concentrated. The crude material was purified by flash chromatography. Elution with ether-hexane (1:9) gave methyl ether **128** (172 mg, 0.827 mmol, 91% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.00 (s, 3H, -CH_3), 1.12 (s, 3H, -CH_3), 1,74 (bs, 3H, vinylic CH_3), 1.80 (m, 1H, C-1 CH), 1.84 (dd, 1H, J = 20, 4 Hz, C-2 CH_2), 2.06 (d, 1H, J = 19 Hz, C-7 CH_2), 2.52 (dd, 1H, J = 20, 4 Hz, C-2 CH_2), 2.56 (dd, 1H, J = 19, 8 Hz, C-7 CH_2), 3.34 (s, 3H, -OCH_3), 3.46 (d, 1H, J = 9 Hz, -CH_2O-), 3.81 (d, 1H, J = 9 Hz, -CH_2O-), and 5.53 (bs, 1H, =CH-); ir 1725 cm^{-1} (C=O); ms M^+ 208.1431 (calcd. for $C_{13}H_{20}O_2$: 208.1463).

7-*endo*-Ethynyl-7-*exo*-hydroxy-1-methoxymethyl-2,8,8-trimethylbicyclo[3.2.1]oct-2-ene (129) and 7-*exo*-Ethynyl-7-*endo*-hydroxy-1-methoxymethyl-2,8,8-trimethyl-bicyclo[3.2.1]-oct-2-ene (130)



129

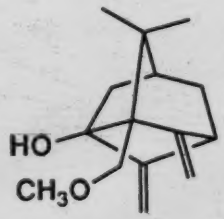


130

To a solution of 2 *M* ethylmagnesium bromide (2 mL, 4 mmol), was added tetrahydrofuran (2 mL). The solution was cooled to 0°C and a stream of acetylene gas was introduced into the solution for 20 min. Then a solution of ketone **128** (57 mg, 0.274 mmol) in benzene (2 mL) was slowly added. After stirring at 0°C for 4 h and at room temperature for 18 h, the mixture was poured into aqueous ammonium chloride solution (30 mL) and extracted with methylene chloride (3 x 20 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with ether-hexane (1:9) gave alcohol **129** (31 mg, 0.132 mmol, 48% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.98 (s, 3H, -CH_3), 1.27 (s, 3H, -CH_3), 1.78 (m, 1H, C-5 C**H**), 1.85 (d, H, J = 17 Hz, C-4 CH_2), 1.90 (bs, 3H, vinylic CH_3), 2.12 (d, 1H, J = 15 Hz, C-6 CH_2), 2.32 (d, 1H, J = 17 Hz, C-4 CH_2), 2.38 (s, 1H, -C≡C**H**), 2.56 (dd, 1H, J = 15, 6.5 Hz, C-6 CH_2), 3.37 (s, 3H,

-OCH_3), 3.40 (s, 1H, -OH), 3.60 (d, 1H, J = 11 Hz, -CH_2O-), 3.70 (d, 1H, J = 11 Hz, -CH_2O-), and 5.34 (bs, 1H, =CH-); ir 3520 (OH), 3300 (OH), and 2100 cm^{-1} (C≡C); ms M^+ 234.1608 (calcd. for $C_{15}H_{22}O_2$: 234.1619). Further elution with ether-hexane (1.5:8.5) afforded another epimer **130** (24 mg, 0.103 mmol, 37% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 1.08 (s, 3H, -CH_3), 1.28 (s, 3H, -CH_3), 1.66 (m, 1H, C-5 CH), 1.74 (d, 1H, J = 15 Hz, C-6 CH_2), 1.89 (bs, 3H, vinylic CH_3), 1.90 (d, 1H, J = 17 Hz, C-4 CH_2), 2.37 (d, 1H, J = 17 Hz, C-4 CH_2), 2.66 (s, 1H, -C≡CH), 2.70 (s, 1H, -OH), 2.82 (ddd, 1H, J = 15, 7, 2 Hz, C-6 CH_2), 3.35 (s, 3H, -OCH_3), and 5.57 (bs, 1H, =CH-); ^{13}C nmr (50 MHz, $CDCl_3$) δ 22.60, 25,30, 34.26, 43.65, 43.95, 49.56, 58.30, 58.85, 72.57, 73.11, 76.32, 81.69, 88.46, 123.63, and 138.45; ir 3480 (OH), 3300 (OH), and 2360 cm^{-1} (C≡C); ms (CI) $(M + NH_4)^+$ 252 (calcd. for $C_{15}H_{26}NO_2$: 252.19).

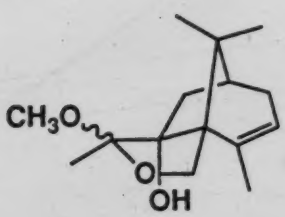
7-Hydroxy-3-methoxymethyl-2,2-dimethyl-4,6-dimethylidene-tricyclo[3.3.1.$0^{3,7}$]nonane (133)



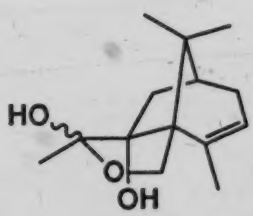
To a solution of compound **129** (9 mg, 0.038 mmol) in methanol (3 mL), were added mercury(II) chloride (10 mg) and 1 *N* aqueous hydrochloric acid (0.25 mL). After stirring at room temperature for 2 h, the mixture was poured into aqueous ammonium chloride solution and

poured into aqueous ammonium chloride solution and extracted with methylene chloride (3 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (1:9) gave compound **133** (7 mg, 78% yield): ^{1}H nmr (300 MHz, $CDCl_3$) δ 0.94 (s, 3H, -CH_3), 1.08 (s, 3H, -CH_3), 1.53 (ddd, 1H, J = 12, 3, 3 Hz, C-9 CH_2), 1.80 (d, 1H, J = 11 Hz, C-8 CH_2), 1.81 (m, 1H, C-1 CH), 2.02 (dddd, 1H, J = 12, 5.5, 3, 3 Hz, C-9 CH_2), 2.47 (ddd, 1H, J = 11, 4, 3 Hz, C-8 CH_2), 3.07 (dd, 1H, J = 3, 3 Hz, C-5 CH), 3.26 (s, 1H, -OH), 3.33 (s, 3H, -OCH_3), 3.59 (d, 1H, J = 9.5 Hz, -CH_2O-), 3.70 (d, 1H, J = 9.5 Hz, -CH_2O-), 4.43, 4.58, 4.75, and 4.86 (all s, 1H each, =CH_2); ^{13}C nmr (APT, 75 MHz, $CDCl_3$) δ 23.13 (q), 25.48 (q), 35.71 (t), 46.27 (d), 46.32 (t), 47.66 (s), 51.47 (d), 59.34 (q), 66.38 (s), 69..66 (t), 86.72 (s), 93.99 (t), 99.36 (t), 135.15 (s), and 162.41 (s); ir 3400 (OH), 1675, and 1660 cm^{-1} (C=C); ms M^+ 234.1616 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

3-Hydroxy-4-methoxy-5-oxa-4,8,11,11-tetramethyl-tricyclo[5.3.1.0^{3,7}]undec-8-enes (134) and 3,4-dihydroxy-5-oxa-4,8,11,11-tetramethyl-tricyclo[5.3.1.0^{3,7}]undec-8-ene (135)



134

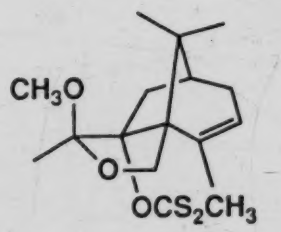


135

To a solution of compound **130** (15 mg, 0.064 mmol) in methanol (5 mL), were added mercury(II) chloride (20 mg) and 1 *N* aqueous hydrochloric acid (0.25 mL). After stirring at room temperature for 4 h, the mixture was poured into aqueous ammonium chloride solution and extracted with methylene chloride (3 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with ether-hexane (1:4) gave *cis*-**134** (2 mg, 0.0079 mmol, 12% yield): ^{1}H nmr (400 MHz, $CDCl_3$) δ 1.00 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3), 1.35 (s, 3H, -CH_3), 1.65 (bs, 3H, vinylic CH_3), 1.70 (m, 1H, C-1 C**H**), 1.76 (ddd, 1H, *J* = 19 Hz, C-10 CH_2), 2.02 (d, 1H, *J* = 16 Hz, C-2 CH_2), 2.36 (ddd, 1H, *J* = 19 Hz, C-10 CH_2), 2.42 (d, 1H, *J* = 16 Hz, C-2 CH_2), 2.80 (s, 1H, D_2O exchangeable, -O**H**), 3.32 (s, 3H, -OCH_3), 3.71 (d, 1H, *J* = 10 Hz, -CH_2O-), 3.82 (d, 1H, *J* = 10 Hz, -CH_2O-), and 5.52 (bs, 1H, =C**H**-). Further elution with ether-hexane (1:3) afforded *trans*-**134** (6 mg, 0.024 mmol, 37% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.95 (s, 3H, -CH_3), 1.04 (s, 3H, -CH_3), 1.40 (s, 3H, -CH_3), 1.56 (bs, 3H, vinylic CH_3), 1.56 (d, 1H, *J* = 14 Hz, C-2 CH_2), 1.68 (dd, 1H, *J* = 6, 6 Hz, C-1 C**H**), 2.03 (d, 1H, *J* = 18 Hz, C-10 CH_2), 2.39 (ddd, 1H, *J* = 18, 6, 1.5 Hz, C-10 CH_2), 2.45 (ddd, 1H, *J* = 14, 6, 1.5 Hz, C-2 CH_2), 3.30 (s, 3H, -OCH_3), 3.48 (d, 1H, *J* = 10 Hz, -CH_2O-), 3.76 (d, 1H, *J* = 10 Hz, -CH_2O-), 4.00 (s, 1H, D_2O exchangeable, -O**H**), and 5.40 (bs, 1H, =C**H**-); ir 3500 and 3300 cm^{-1} (OH); ms M^+ 252.1717 (calcd. for $C_{15}H_{24}O_3$: 252.1725). Further elution with ether-hexane (2:3) gave rise to compound **135** (6 mg, 0.025 mmol, 39% yield): ^{1}H nmr (400

MHz, $CDCl_3$) δ 1.04 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 1.54 (s, 3H, -COH(CH_3)-), 1.56 (d, 1H, *J* = 14 Hz, C-6 CH_2), 1.68 (bs, 3H, vinylic CH_3), 1.80 (dd, 1H, *J* = 6, 6 Hz, C-7 CH), 2.07 (d, 1H, *J* = 18 Hz, C-8 CH_2), 2.49 (dddd, 1H, *J* = 18, 6, 4, 2 Hz, C-8 CH_2), 2.60 (ddd, 1H, *J* = 14, 6, 2 Hz, C-6 CH_2), 3.60 (s, 1H, D_2O exchangeable, -OH), 3.69 (d, 1H, *J* = 9.5 Hz, -CH_2O-), 4.01.(d, 1H, *J* = 9.5 Hz, -CH_2O-), 5.10.(s, 1H, D_2O exchangeable, -OH), and 5.60 (bs, 1H, =CH-).

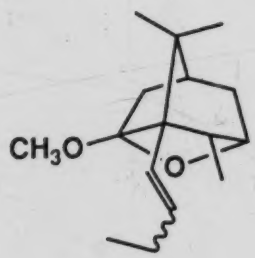
4-Methoxy-3-(methylthio)thiocarbonyloxy-5-oxa-4,8,11,11-tetramethyltricyclo[5.3.1.$0^{1,5}$]undec-8-ene (136)



To a solution of *trans*-**134** (18 mg, 0.071 mmol) in dimethoxyethane (5 mL), were added sodium hydride (50% pure, 10 mg, 0.21 mmol), carbon disulfide (0.1 mL) and iodomethane (0.1 mL). After stirring at room temperature for 6 h, the mixture was poured into brine (30 mL) and extracted with ether (3 x 10 mL). The extracts were dried, filtered and concentrated. Purification of the crude material by flash chromatography (ether-hexane 1:10) gave compound **136** (12 mg, 0.035 mmol, 49% yield): ^{1}H nmr (300 MHz, $CDCl_3$) δ 0.99 (s, 3H, -CH_3), 1.08 (s, 3H, -CH_3), 1.70 (ddd, 3H, *J* = 2, 2, 2 Hz, vinylic CH_3), 1.72 (s, 3H, C-4 CH_3), 1,82 (dd, 1H, *J* = 5.5, 5.5 Hz, C-1 CH), 1.95 (dd, 1H, *J* = 18, 2 Hz, C-10

CH_2), 2.39 (dddd, 1H, J = 18, 5.5, 2, 2 Hz, C-10 CH_2), 2.48 (s, 3H, -SCH_3), 2.65 (ddd, 1H, J = 16, 5.5, 2 Hz, C-2 CH_2), 2.69 (d, 1H, J = 16 Hz, C-6 CH_2), 3.21 (s, 3H, -OCH_3), 3.59 (d, 1H, J = 9 Hz, -CH_2O-), 3.95 (d, 1H, J = 9 Hz, -CH_2O-), and 5.36 (bs, 1H, =CH-); ir 1241 cm^{-1} (C=S); ms M^+ 342.1325 (calcd. for $C_{17}H_{26}O_3S_2$: 342.1323).

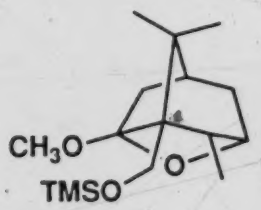
3-(1-Butenyl)-7-methoxy-6-oxa-2,2,4-trimethyltricyclo-[3.3.1.$0^{3,7}$]nonane (142)



Under an argon atmosphere, a 2 *M* butyllithium solution (0.5 mL, 1.0 mmol) was added to a mixture of triphenylpropylphosphonium chloride and tetrahydrofuran (5 mL). After the mixture had been stirred for 5 min, a solution of aldehyde **140** (139 mg, 0.62 mmol) in tetrahydrofuran (2 mL) was added dropwise. After stirring at room temperature for 18 h, the mixture was poured into water (50 mL) and extracted with ether (3 x 25 mL). The extracts were dried, filtered and concentrated. The crude product was purified by flash chromatography. Elution with ether-hexane (1:5) gave compound **142** (109 mg, 0.436 mol, 70% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.87 (s, 3H, -CH_3), 0.97 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.03 (t, 3H, J = 7.5 Hz, -CH_2CH_3), 1.13 (s, 3H, -CH_3), 1.65 (ddd, 1H, J = 14.0, 3.5, 3.5 Hz, C-9 CH_2), 1.76 (ddd, 1H, J = 14.0 Hz, C-9 CH_2), 1.83 (m, 1H, C-1 CH), 2.00 (d, 1H, J = 11 Hz,

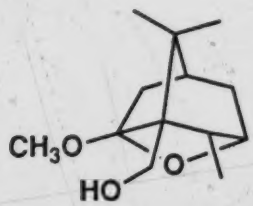
1.83 (m, 1H, C-1 CH), 2.00 (d, 1H, J = 11 Hz, C-8 CH_2), 2.11 (dq, 2H, J = 4.0, 7.5 Hz, -CH_2CH_3), 2.20 (ddd, 1H, J = 11, 4, 1.5 Hz, C-8 CH_2), 2.68 (q, 1H, J = 6.5 Hz, -$CH(CH_3)$-), 3.45 (s, 3H, -OCH_3), 4.06 (d, 1H, J = 3.5 Hz, -CHO-), and 5.44 (complex, 2H, -CH=CH-); ms M^+ 250.1931 (calcd. for $C_{16}H_{26}O_2$: 250.1933).

7-Methoxy-2,4,4-trimethyl-3-trimethylsiloxymethyl-6-oxatricyclo[3.3.1.$0^{3,7}$]nonane (138)



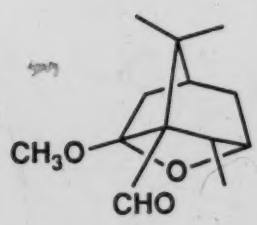
In a similar procedure to the one for compound **128** using sodium hydride (453 mg, 9.8 mmol) and iodomethane (0.61 mL, 9.8 mmol), methylation of alcohol **111a** (2.329 g, 8.20 mmol) gave cyclic acetal **138** (2.253 g, 7.56 mmol, 92% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.08 (s, 9H, -$Si(CH_3)_3$), 1.03 (d, 3H, J = 7 Hz, -$CH(CH_3)$-), 1.10 (s, 3H, -CH_3), 1.19 (s, 3H, -CH_3), 1.60 (ddd, 1H, J = 13, 4, 3 Hz, C-9 CH_2), 1.74 (ddd, 1H, J = 13, 4, 1.5 Hz, C-9 CH_2), 1.78 (m, 1H, C-1 CH), 1.97 (d, 1H, J = 10 Hz, C-8 CH_2), 2.12 (ddd, 1H, J = 10, 4, 1.5 Hz, C-8 CH_2), 2.54 (q, 1H, J = 7 Hz, -$CH(CH_3)$-), 3.63 (d, 1H, J = 16 Hz, -CH_2O-), 3.64 (d, 1H, J = 16 Hz, -CH_2O-), 3.39 (s, 3H, -OCH_3), and 4.02 (d, 1H, J = 4 Hz, -CHO-); no ir absorption for C=O ; ms M^+ 298.1966 (calcd. for $C_{16}H_{30}O_3Si$: 298.1964).

3-Hydroxymethyl-7-methoxy-2,2,4-trimethyl-6-oxa-tricyclo[3.3.1.0^{3,7}]nonane (139)



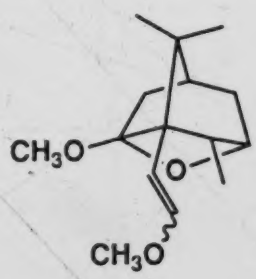
In a similar procedure to the one for compound **118** using potassium fluoride (1.0 g) and methanol (15 mL), desilylation of compound **138** (2.253 g, 7.56 mmol) gave alcohol **139** (1.696 g, 7.50 mmol, 99% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.10 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.14 (s, 3H, -CH_3), 1.20 (s, 3H, -CH_3), 1.36 (bs, 1H, -OH), 1.60 (ddd, 1H, J = 14, 3.5, 3.5 Hz, C-9 CH_2), 1.76 (ddd, 1H, J = 14, 4, 1.5 Hz, C-9 CH_2), 1.80 (m, 1H, C-1 CH), 2.00 (d, 1H, J = 11 Hz, C-8 CH_2), 2.14 (ddd, 1H, J = 11, 4, 1.5 Hz, C-8 CH_2), 2.52 (q, 1H, J = 6.5 Hz, -CH(CH_3)-), 3.40 (s, 3H, -OCH_3), 3.78 (d, 1H, J = 16 Hz, -CH_2O-), 3.80 (d, 1H, J = 16 Hz, -CH_2O-), and 4.03 (d, 1H, J = 3.5 Hz, -CHO-); ir 3503 cm^{-1} (OH).

3-Formyl-7-methoxy-2,2,4-trimethyl-6-oxatricyclo[3.3.1.0^{3,7}]-nonane (140)



In a similar procedure to the one for compound **99** using oxalyl chloride (0.186 mL, 2.13 mmol), DMSO (0.14 mL, 2.13 mmol) and triethylamine (0.595 mL, 4.26 mmol), oxidation of alcohol **139** (371 mg, 1.64 mmol) gave aldehyde **140** (342 mg, 1.53 mmol, 93% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.09 (s, 3H, -CH_3), 1.16 (s, 3H, -CH_3), 1.68 (ddd, 1H, J = 14, 3.5, 3.5 Hz, C-9 CH_2), 1.76 (ddd, 1H, J = 14, 3, 1.5 Hz, C-9 CH_2), 1.90 (ddd, 1H, J = 4.5, 3.5, 3 Hz, C-1 CH), 2.15 (d, 1H, J = 11 Hz, C-8 CH_2), 2.38 (ddd, 1H, J = 11, 4.5, 1.5 Hz, C-8 CH_2), 2.58 (q, 1H, J = 6.5 Hz, -CH(CH_3)-), 3.54 (s, 3H, -OCH_3), 4.07 (d, 1H, J = 3.5 Hz, -CHO-), and 9.82 (s, 1H, -CHO).

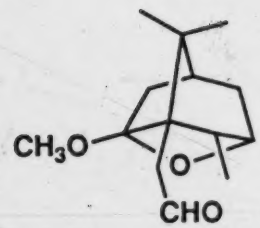
7-Methoxy-3-methoxyvinyl-2,2,4-trimethyl-6-oxatricyclo-[3.3.1.0^{3,7}]nonane (144)



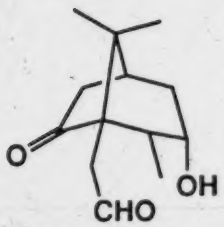
In a similar procedure to the one for compound **120** using a 2 *M* butyllithium solution (1.14 mL) and methoxymethyltriphenylphosphonium chloride (1.044 g), Wittig reaction of compound **140** (342 mg, 1.527 mmol) gave rise to *cis*-**144** (234 mg, 0.929 mmol, 61% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.89 (s, 3H, -CH_3), 0.96 (d, 1H, J = 7 Hz,

-CH(CH_3)-), 1.16 (s, 3H, -CH_3), 1.62 (ddd, 1H, J = 14, 3.5, 3.5 Hz, C-9 CH_2), 1.75 (ddd, 1H, J = 14, 2 Hz, C-9 CH_2), 1.77 (m, 1H, C-1 CH), 1.98 (d, 1H, J = 11 Hz, C-8 CH_2), 2.15 (ddd, 1H, J = 11, 4.5, 2 Hz, C-8 CH_2), 2.73 (q, 1H, J = 7 Hz, -CH(CH_3)-), 3.47 (s, 3H, acetal-OCH_3), 3.56 (s, 3H, vinylic OCH_3), 4.02 (d, 1H, J = 3.5 Hz, -CHO-), 5.42 (d, 1H, J = 7 Hz, -CH=CHOCH_3), and 5.89 (d, 1H, J = 7 Hz, -CH=CHOCH_3), and *trans*-**144** (121 mg, 0.480 mmol, 31% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.88 (s, 3H, -CH_3), 0.98 (d, 1H, J = 7 Hz, -CH(CH_3)-), 1.01 (s, 3H, -CH_3), 1.67 (ddd, 1H, J = 13, 3.5, 3.5 Hz, C-9 CH_2), 1.86 (ddd, 1H, J = 13, 3, 1.5 Hz, C-9 CH_2), 1.89 (m, 1H, C-1 CH), 2.03 (d, 1H, J = 11 Hz, C-8 CH_2), 2.20 (ddd, 1H, J = 11, 4.5, 1.5 Hz, C-8 CH_2), 2.38 (q, 1H, J = 7 Hz, -CH(CH_3)-), 3.48 (s, 3H, -OCH_3), 3.57 (s, 3H, vinylic OCH_3), 4.05 (d, 1H, J = 3.5 Hz, -CHO-), 4.83 (d, 1H, J = 14 Hz, -CH=CHOCH_3), and 5.30 (d, 1H, J = 14 Hz, -CH=CHOCH_3); ir 1660 cm^{-1} (C=C); ms M^+ 252.1725 (calcd. for $C_{15}H_{24}O_3$: 252.1725).

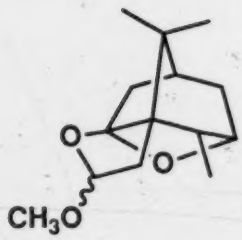
7-Methoxy-2,2,4-trimethyl-6-oxa-3-(2-oxoethyl)tricyclo-[3.3.1.$0^{3,7}$]nonane (145), 3-Hydroxy-4,8,8-trimethyl-5-(2-oxoethyl)bicyclo[3.2.1]octan-6-one (146), and 5-methoxy-8,11,11-trimethyl-4,12-dioxatetracyclo[5.3.1.$1^{3,9}$.$0^{3,7}$]-dodecane (147)



145



146

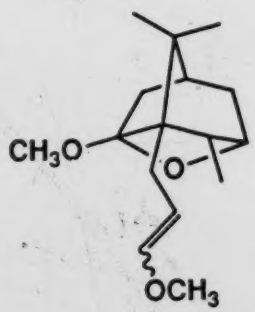


147

To a solution of compound **144** (304 mg, 1.206 mmol) in ether (3 mL), was added 35% aqueous perchloric acid (3 mL). After stirring at room temperature for 20 min, the mixture was poured into an aqueous sodium bicarbonate solution (40 mL) and extracted with methylene chloride (3 x 15 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was subjected to flash chromatography. Elution with ether-hexane (1:4) gave rise to cyclic acetal **147** (29 mg, 0.121 mmol, 10% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.04 (d, 3H, J = 7 Hz, -CH(C**H**$_3$)-), 1.07 (s, 3H, -C**H**$_3$), 1.12 (s, 3H, -C**H**$_3$), 1.70 (dd, 1H, J = 13, 2.5 Hz, C-10 C**H**$_2$), 1.73 (m, 1H, C-1 C**H**), 1.76 (ddd, 1H, J = 13, 4, 1.5 Hz, C-10 C**H**$_2$), 2.02 (d, 1H, J = 12 Hz, C-2 C**H**$_2$), 2.03 (dd, 1H, J = 19, 6 Hz, C-6 C**H**$_2$), 2.07 (dd, 1H, J = 19, 5.5 Hz, C-6 C**H**$_2$), 2.23 (ddd, 1H, J = 12, 4, 1.5 Hz, C-2 C**H**$_2$), 2.42 (q, 1H, J = 7 Hz, -C**H**(CH$_3$)-, 3.47 (s, 3H, -OC**H**$_3$), 4.13 (m, 1H, -C**H**O-), and 5.40 (dd, 1H, J = 6, 5.5 Hz, -OC**H**O-); no ir absorption for either C=O or OH; ms M$^+$ 238.1570 (calcd. for $C_{14}H_{22}O_3$: 238.1569). Further eluton with ether-hexane (1:3) gave aldehyde **145** (178 mg, 0.748 mmol, 62% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.98 (s, 3H, -C**H**$_3$), 1.05 (d, 1H, J = 7 Hz, -CH(C**H**$_3$)-), 1.10 (s, 3H, -C**H**$_3$), 1.64 (ddd, 1H, J = 12, 4, 2

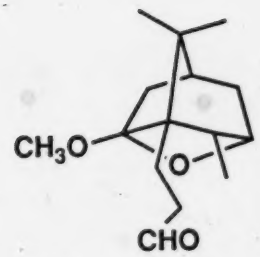
Hz, C-9 CH_2), 1.78 (ddd, 1H, J = 12, 4, 2 Hz, C-9 CH_2), 1.82 (m, 1H, C-1 CH), 2.05 (d, 1H, J = 11 Hz, C-8 CH_2), 2.12 (ddd, 1H, J = 11, 4, 2 Hz, C-8 CH_2), 2.50 (dd, 1H, J = 17, 3.5 Hz, -CH_2CHO), 2.55 (dd, 1H, J = 17, 2 Hz, -CH_2CHO), 2.65 (q, 1H, J = 7 Hz, -CH(CH_3)-), 3.45 (s, 3H, -OCH_3), 4.07 (d, 1H, J = 4 Hz, -CHO-), and 9.90 (dd, 1H, J = 3.5, 2 Hz, -CHO); ir 1721 cm^{-1} (C=O); ms M^+ 238.1563 (calcd. for $C_{14}H_{22}O_3$: 238.1568). Further elution with ether-hexane (2:3) gave hydroxy aldehyde **146** (67 mg, 0.30 mmol, 25% yield): ^1H nmr (200 MHz, $CDCl_3$) δ 1.00 (s, 3H, -CH_3), 1.08 (d, 1H, -CH(CH_3)-), 1.20 (s, 3H, -CH_3), 1.73 (bs, 1H, -OH), 1.87 (dd, 1H, C-2 CH_2), 2.02 (ddd, 1H, C-2 CH_2), 2.04 (m, 1H, C-1 CH), 2.30 (dd, 1H, C-7 CH_2), 2.40 (dd, 1H, -CH_2CHO), 2.65 (dq, 1H, -CH(CH_3)-), 2.78 (d, 1H, C-7 CH_2), 2.84 (dd, 1H, -CH_2CHO), 4.00 (dd, 1H, -CHOH), and 9.92 (dd, 1H, -CHO); ir 3460 (OH), 1735 (C=O), and 1719 cm^{-1} (C=O); ms M^+ 224.1406 (calcd. for $C_{13}H_{20}O_3$: 224.1412).

7-Methoxy-8-(3-methoxyallyl)-2,2,4-trimethyl-6-oxa-tricyclo[3.3.1.$0^{3,7}$]nonane (148)



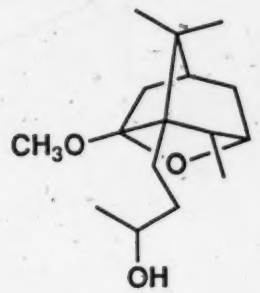
In a similar procedure to the one for compound **120** using a 2 *M* butyllithium solution (0.27 mL, 0.536 mmol) and methoxymethyltriphenylphosphonium chloride (122 mg, 0.714 mmol), Wittig reaction of compound **145** (85 mg, 0.357 mmol) gave a mixture of *cis* and *trans*-**148** (80 mg, 0.300 mmol, 84% yield). The isomers were partially separated by further flash chromatography (ether-hexane 1:4). *cis*-**148**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J* = 6.5 Hz, -CH(CH_3)-), 1.04 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3), 1.60 (ddd, 1H, *J* = 14, 4, 4 Hz, C-9 CH_2), 1.72 (m, 1H, C-1 CH), 1.74 (d, 1H, *J* = 14 Hz, C-9 CH_2), 2.00 (d, 1H, *J* = 11 Hz, C-8 CH_2), 2.08 (ddd, 1H, *J* = 20, 9, 2.5Hz, C-1' CH_2), 2.10 (ddd, 1H, *J* = 11, 4, 1.5 Hz, C-8 CH_2), 2.14 (ddd, 1H, *J* = 20, 5, 1.5 Hz, C-1' CH_2), 2.46 (q, 1H, *J* = 6.5 Hz, -CH(CH_3)-, 3.43 (s, 3H, -OCH_3), 3.62 (s, 3H, -C=CHOCH_3), 3.99 (d, 1H, -CH(O-)-), 4.41 (ddd, 1H, *J* = 6, 9, 5 Hz, -CH=CHOCH_3), and 5.90 (ddd, 1H, *J* = 6, 2.5, 1.5 Hz, -CH=CHOCH_3). *trans*-**148**: ^{1}H nmr (200 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J* = 6.5 Hz, -CH(CH_3)-), 1.04 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3), 1.60 (ddd, 1H, *J* = 14, 4, 4 Hz, C-9 CH_2), 1.72 (m, 1H, C-1 CH), 1.74 (d, 1H, *J* = 14 Hz, C-9 CH_2), 2.00 (d, 1H, *J* = 11 Hz, C-8 CH_2), 2.08 (ddd, 1H, *J* = 20, 9, 1 Hz, C-1' CH_2), 2.10 (ddd, 1H, *J* = 11, 4, 1.5 Hz, C-8 CH_2), 2.14 (ddd, 1H, *J* = 20, 5.5, 1.5 Hz, C-1' CH_2), 2.46 (q, 1H, *J* = 6.5 Hz, -CH(CH_3)-), 3.44 (s, 3H, -OCH_3), 3.54 (s, 3H, =CHOCH_3), 3.99 (d, 1H, -CHO-), 4.74 (ddd, 1H, *J* = 12, 9, 5.5 Hz, -CH=CHOCH_3), and 6.32 (ddd, 1H, *J* = 12, 1.5, 1 Hz, -CH=CHOCH_3).

7-Methoxy-2,2,4-trimethyl-6-oxa-3-(3-oxopropyl)tricyclo-[3.3.1.0^{3,7}]-nonane (149)



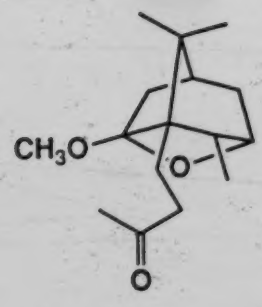
To a solution of compound **148** (125 mg, 0.47 mmol) in ether (3 mL), was added 35% aqueous perchloric acid (3 mL). After stirring at room temperature for 20 min, the mixture was poured into an aqueous sodium bicarbonate solution (40 mL) and extracted with methylene chloride (3 x 15 mL). The extracts were washed with water, dried, filtered and concentrated. The crude product was subjected to flash chromatography. Elution of ether-hexane (1:9) resulted in partial recovery of starting material (18 mg, 14%). Further elution with ether-hexane (1:3) afforded aldehyde **149** (76 mg, 0.30 mmol, 63% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, J = 6.5 Hz, -CH(CH_3)-), 1.06 (s, 3H, -CH_3), 1.16 (s, 3H, -CH_3), 1.61 (ddd, 1H, J = 14, 3.5, 3.5 Hz, C-9 CH_2), 1.65 (ddd, 1H, J = 15, 12, 6 Hz, C-1' CH_2), 1.72 (ddd, 1H, J = 14, 4, 1.5 Hz, C-9 CH_2), 1.77 (m, 1H, C-1 CH), 1.81 (ddd, 1H, J = 15, 12, 4 Hz, C-1' CH_2), 2.00 (d, 1H, J = 11 Hz, C-8 CH_2), 2.08 (ddd, 1H, J = 11, 4, 1.5 Hz, C-6 CH_2), 2.32 (dddd, 1H, J = 16, 12, 4, 2 Hz, C-2' CH_2), 2.41 (q, 1H, J = 6.5 Hz, -CH(CH_3)-), 2.52 (dddd, 1H, J = 16, 12, 6, 2 Hz, C-2' CH_2), 3.43 (s, 3H, -OCH_3), 3.98 (d, 1H, -CHO), and 9.74 (dd, 1H, J = 2, 2 Hz, -CHO); ir 1725 cm^{-1} (C=O); ms M^+ 252.1719 (calcd. for $C_{15}H_{24}O_3$: 252.1725).

3-(3-Hydroxybutyl)-7-methoxy-2,2,4-trimethyl-6-oxatricyclo-[3.3.1.0^{3,7}]nonanes (150)



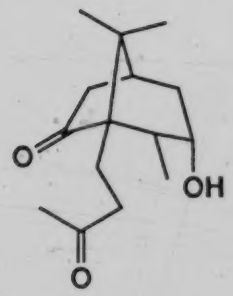
In a similar procedure to the one for compound **122** using a 1*M* methyllithium solution (0.2 mL), the addition reaction of aldehyde **149** into methyllithium gave a 1:1 epimeric mixture of alcohol **150** (30 mg, 0.112 mmol, 94% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.97 / 1.00 (d, 3H, *J* = 7 Hz, -CH(CH_3)-), 1.04 / 1.06 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3), 1.20 / 1.21 (d, 3H, *J* = 6.5 Hz, -CHOHCH_3), 1.3-1.8 (complex, 8H), 1.99 (d, 1H, *J* = 11 Hz), 2.08 (bd, 1H, *J* = 11 Hz), 2.41 (q, 1H, *J* = 7 Hz, -CH(CH_3)-), 3.42 (s, 3H, -OCH_3), 3.75 (bs, 1H, -CHOH), and 3.95 (d, 1H, *J* = 2 Hz, -CHO-).

7-Methoxy-2,2,4-trimethyl-6-oxa-3-(3-oxobutyl)tricyclo-[3.3.1.0^{3,7}]nonane (151)



In a similar procedure to the one for compound **99** using oxalyl chloride (0.10 mL), DMSO (0.07 mL) and triethylamine (0.30 mL), oxidation of compound **150** (30 mg, 0.112 mmol) gave ketone **151** (25 mg, 0.094 mmol, 84% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.97 (d, 3H, J = 7 Hz, -CH(CH_3)-), 1.04 (s, 3H, -CH_3), 1.15 (s, 3H, -CH_3), 1.60 (ddd, 1H, J = 13, 4, 4 Hz, C-9 CH_2), 1.5-1.8 (complex, 4H), 1.98 (d, 1H, J = 11 Hz, C-8 CH_2), 2.07 (ddd, 1H, J = 11, 4, 2 Hz, C-8 CH_2), 2.17 (s, 3H, -$COCH_3$), 2.31 (ddd, 1H, J = 16, 11, 4 Hz, -CH_2COCH_3), 2.38 (q, 1H, J = 7 Hz, -CH(CH_3)-), 2.50 (ddd, 1H, J = 16, 12, 6.5 Hz, -CH_2COCH_3), 3.43 (s, 3H, -OCH_3), and 3.98 (d, 1H, J = 3.5 Hz, -CHO-); ir 1716 cm^{-1} (C=O); ms M^+ 266.1882 (calcd. for $C_{16}H_{26}O_3$: 266.1882).

3-Hydroxy-4,8,8-trimethyl-5-(3-oxobutyl)bicyclo[3.2.1]-octan-6-one (152)



To a solution of cyclic acetal **151** (40 mg, 0.15 mmol) in ether (3 mL), was added 72% perchloric acid (1 mL). After stirring for 20 min, the mixture was poured into an aqueous sodium bicarbonate solution (30 mL) and extracted with methylene chloride (3 x 10 mL). The extracts were washed with water, dried, filtered and concentrated. The residue was subjected to flash chromatography. Elution with ether-hexane (2:3) gave rise to hydroxy diketone **152** (25 mg, 0.099 mmol, 66% yield): ^{1}H nmr (200 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 7.5 Hz, -CH(C**H**$_3$)-), 0.95 (s, 3H, -C**H**$_3$), 1.18 (s, 3H, -C**H**$_3$), 1.24 (bs, 1H, -O**H**), 1.49 (ddd, 1H, J = 19, 11, 6 Hz, C-1' C**H**$_2$), 1.81 (ddd, 1H, J = 14, 3, 1 Hz, C-2 C**H**$_2$), 1.88 (dd, 1H, J = 7, 3 Hz, C-1 C**H**), 2.05 (ddd, 1H, J = 19, 12, 4.5 Hz, C-1' C**H**$_2$), 2.15 (s, 3H, -COC**H**$_3$), 2.25 (ddd, 1H, J = 18, 7, 1 Hz, C-7 C**H**$_2$), 2.27 (ddd, 1H, J = 16, 11, 4.5 Hz, -C**H**$_2$COCH$_3$), 2.32 (q, 1H, J = 7.5 Hz, -C**H**(CH$_3$)-), 2.32 (d, 1H, J = 14 Hz, C-2 C**H**$_2$), 2.42 (ddd, 1H, J = 16, 12, 6 Hz, -C**H**$_2$COCH$_3$), 2.67 (d, 1H, J = 18 Hz, C-7 C**H**$_2$), and 4.00 (bs, 1H, -C**H**(OH)-); ir 3440 (OH), 1734 (C=O), and 1715 cm^{-1} (C=O); ms M$^+$ 252.1723 (calcd. for $C_{15}H_{24}O_3$: 252.1725).

Coupling reaction experiment of diketo alcohol 152

Under an argon atmosphere, titanium trichloride (140 mg, 0.91 mmol) and potassium metal (135 mg, 3.45 mmol) were placed in a flask with dimethoxyethane (20 mL). The mixture was heated under reflux for 2 h. Then the solution of compound **152** (25 mg, 0.099 mmol) in dimethoxyethane (2 mL) was added in portions over a period of 5 h. The reaction mixture was further refluxed for 24 h and then cooled to room temperature. The reaction was quenched by slow addition of ethanol (5 mL) with stirring. After addition of diethyl ether (30 mL), the resulting mixture was filtered through sintered glass, and the filtrate was washed with saturated aqueous sodium chloride solution (2 x 20 mL), dried and concentrated. Flash chromatography of the residue on silica gel afforded no identifiable product. The reaction was also carried out using tetrahydrofuran as a solvent in place of dimethoxyethane. No identifiable product was obtained.

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